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REVIEW

Development of Organ-Specific Donor Risk Indices

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Because of the shortage of deceased donor organs, transplant centers accept organs from marginal deceased donors, including older donors. Organ-specific donor risk indices have been developed to predict graft survival with various combinations of donor and recipient characteristics. Here we review the kidney donor risk index (KDRI) and the liver donor risk index (LDRI) and compare and contrast their strengths, limitations, and potential uses. The KDRI has a potential role in developing new kidney allocation algorithms. The LDRI allows a greater appreciation of the importance of donor factors, particularly for hepatitis C virus–positive recipients; as the donor risk index increases, the rates of allograft and patient survival among these recipients decrease disproportionately. The use of livers with high donor risk indices is associated with increased hospital costs that are independent of recipient risk factors, and the transplantation of livers with high donor risk indices into patients with Model for End-Stage Liver Disease scores < 15 is associated with lower allograft survival; the use of the LDRI has limited this practice. Significant regional variations in donor quality, as measured by the LDRI, remain in the United States. We also review other potential indices for liver transplantation, including donor-recipient matching and the retransplant donor risk index. Although substantial progress has been made in developing donor risk indices to objectively assess donor variables that affect transplant outcomes, continued efforts are warranted to improve these indices to enhance organ allocation policies and optimize allograft survival. ***Liver Transpl 18:395-404, 2012.*** © **2012 AASLD.**

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The demand for organs for kidney and liver transplantation far exceeds the supply of deceased donor organs. Transplant centers are, therefore, forced to consider using allografts from higher risk donors; this need is particularly evident in the geographic areas with the longest waiting times. Allografts may be at

Abbreviations: CI, confidence interval; COD, cause of death; CVA, cerebrovascular accident; DCD, donation after cardiac death; ECD, expanded criteria donor; HCV, hepatitis C virus; HLA, human leukocyte antigen; KDPI, kidney donor profile index; KDRI, kidney donor risk index; LDRI, liver donor risk index; MELD, Model for End-Stage Liver Disease; OPTN, Organ Procurement and Transplantation Network; SCR, serum creatinine; SOFT, survival outcomes following liver transplantation; SRTR, Scientific Registry of Transplant Recipients; UNOS, United Network for Organ Sharing.

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risk for graft failure (which can subsequently lead to the death of recipients) because of factors such as donor age. To quantify this increased risk, donor risk indices were created. Currently, there are no widely accepted donor risk indices for heart and lung donors. Because of the difficulty in defining pancreas allograft survival, assessing a pancreas donor risk index is difficult. We review the history of the development of the kidney donor risk index (KDRI), which led to increasing interest in the liver donor risk index (LDRI), and we speculate on the potential future uses of these indices.

DONOR RISK INDICES IN KIDNEY TRANSPLANTATION

To increase the deceased donor organ pool, transplant centers use kidneys from marginal donors, including older donors. To help clinicians to choose the best kidney allografts for their patients, scoring systems have been developed with various combinations of donor and recipient characteristics to predict expected all-cause allograft failure.

Expanded Criteria Donors (ECDs)

Historically, increasing the donor pool primarily meant using organs from older kidney donors; recent increases involve donation after cardiac death (DCD). In Spain, efforts to improve kidney donation in the 1990s increased the average age of kidney donors by 11 years, and more than 25% of all donors were older than 60 years.[1] Although these methods increased organ donation, the concern arose that kidneys from older donors produced poorer recipient allograft function and survival.[2,3] This led to a dilemma for clinicians: should older kidneys with poor allograft survival be used, or should patients remain on dialysis with its attendant mortality risk?

Expanded criteria donation was introduced in November 2001 in the Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS) policy for deceased donor kidney allocation; the criteria assist clinicians and patients in making decisions about accepting marginal kidneys.[4] The goal was to establish the donor factors that lead to an increased risk of all-cause allograft failure. Port et al.[5] used data from the Scientific Registry of Transplant Recipients (SRTR) to examine first deceased donor kidney-only transplants in the United States from March 1995 to November 2000; they considered the effects of donor factors [age, sex, race, year of donation, diabetes, hypertension, impaired kidney function, and cause of death (COD)] and multiple recipient factors. ECDs were defined as donors whose relative risk of allograft failure was greater than 1.7 in comparison with donors who were 10 to 39 years old, had terminal serum creatinine (SCR) levels $\leq$ 1.5 mg/dL, and had no history of hypertension or cerebrovascular accident (CVA) as the COD. Among these donor characteristics, only age, impaired kidney function (SCR $>$ 1.5 mg/dL), hypertension, and CVA as the COD were independently associated with an increased risk of allograft failure. ECD criteria were defined as an age older than 60 years or an age of 50 to 59 years with 2 or more additional donor risk factors.

Since the reporting of ECDs and the revision of the OPTN/UNOS allocation policy, all candidates must be asked if they wish to be considered for ECD kidney transplantation.[6] This policy requires a separate consent form to inform candidates of the allocation procedures and the potential differences in allograft survival. By consenting to ECD kidneys, candidates decrease the time that they spend on the waiting list in exchange for a higher risk of allograft failure. Despite the increased risk, 43% of the candidates on the waiting list consent to ECD kidneys.[7] Interestingly, in comparison with wait-listed candidates, the overall mortality rate is lower for ECD kidney recipients who are older than 40 years, African American, or Asian.[8] This difference is most notable in regions in which the waiting time exceeds 1350 days; more than 50% of the wait-listed candidates in 23 of the 58 donor service areas in the United States are willing to accept an ECD kidney, as are 80% to 100% in 9 donor service areas.[7]

Donor Variability

The ECD designation does not in itself effectively portray organ quality. Variations within ECDs substantially influence allograft survival in ways that cannot be accurately predicted by a dichotomous variable. Several studies have expanded the donor criteria to provide a more graded approach to allograft quality.

Before ECDs were introduced, Nyberg et al.[9] proposed a donor risk scoring system to identify deceased donor kidneys at the highest risk of early allograft dysfunction. They used 18 risk factors for delayed graft function, including 12 donor factors and 6 recipient factors. Using univariate and multivariate analyses, they developed a scoring system that accounted for the donor's age, COD, history of hypertension and diabetes, creatinine clearance, preservation time, and degree of renal artery plaque. Scores ranged from 0 to 32: grade A was defined as a risk score of 0 to 5, grade B was defined as a risk score of 6 to 10, grade C was defined as a risk score of 11 to 15, and grade D was defined as a risk score $\geq$ 16. In a validation group, they found that creatinine clearance 30 days after transplantation was $>$40 mL/minute for a significantly higher proportion of grade A recipients versus grade D recipients (91% versus 23%). Similarly, delayed graft function was less likely for grade A recipients versus grade D recipients (17% versus 62%).

Nyberg et al.[10] modified their donor risk scoring system in a larger cohort with donor information available at the time of procurement. Using SRTR data, they examined deceased donor kidney transplants with 9 donor variables and 4 recipient

variables. This revised scoring system incorporated the donor's age, history of hypertension, creatinine clearance, number of human leukocyte antigen (HLA) mismatches, and COD. Scores ranged from 0 to 39: grade A was defined as a score of 0 to 9, grade B was defined as a score of 10 to 19, grade C was defined as a score of 20 to 29, and grade D was defined as a score of 30 to 39. Again, a higher percentage of grade A recipients versus grade D recipients experienced good or excellent kidney function at 1 year (creatinine clearance $\geq$ 40 mL/minute: 81% versus 37%). With this system, ECD kidneys could be subdivided into grade C and D kidneys; 56% of grade C recipients experienced good or excellent kidney function, whereas only 37% of grade D recipients did.

To further develop this scoring system, Schold et al.[11] constructed a model focusing on all-cause allograft failure as the endpoint. This model includes the donor's age, race, COD, and history of hypertension and diabetes; donor-recipient cytomegalovirus matching; HLA mismatches; and the cold ischemia time. A donor grade of I to V is assigned to the kidney, and 1- and 5-year allograft survival can be determined.

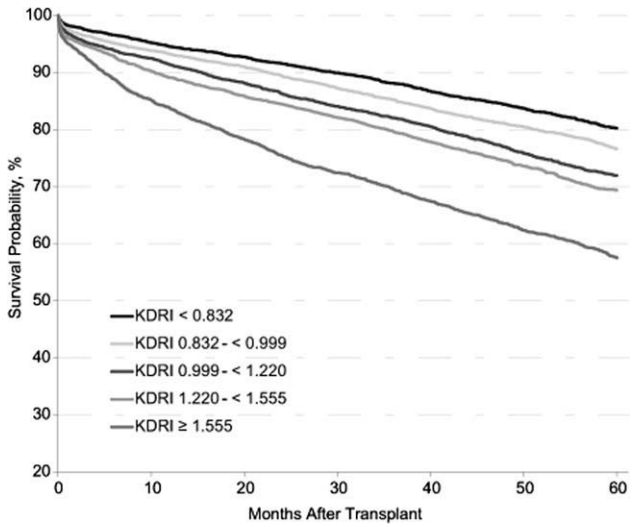

Figure 1. Probability of survival after kidney transplantation for transplant recipients (2005-2006) according to the KDRI values. Only first transplants were included. Multiorgan transplants were excluded, and no adjustments were made for recipient or other donor factors.

KDRI

Derivation

The ECD criteria and the risk scoring systems of Nyberg et al.[9,10] and Schold et al.[11] arbitrarily categorize risk and possibly reduce the accuracy of a risk score. To improve on previous models, the KDRI developed by Rao et al.[12] provides a continuous risk score by avoiding categorized variables in the calculation; the model was developed with SRTR data from January 1, 1995 to December 31, 2005. Their study assessed donor and transplant factors not included in previous donor risk scores: donor height and weight, DCD, cigarette use, hepatitis C virus (HCV), pulsatile perfusion, organ sharing, year of transplantation, en bloc/double transplantation, and ABO compatibility. It also assessed recipient factors, including height, weight, angina pectoris, drug-treated chronic obstructive pulmonary disease, and HCV. The final KDRI includes 14 donor and transplant factors, and each is independently associated with all-cause allograft failure: age, African American race, SCR, hypertension and diabetes, COD, height, weight, DCD, HCV, HLA mismatches, cold ischemia time, en bloc transplantation, and double kidney transplantation. The final score is compared with a reference donor with a KDRI score of 1.00 [ie, a healthy 40-year-old, non–African American, nonhypertensive, nondiabetic, HCV-negative, brain-dead (rather than DCD) donor with an SCR level of 1.0 mg/dL, a height of 170 cm, a weight $\geq$ 80 kg, 2 HLA-B mismatches, 1 HLA-DR mismatch, and a cold ischemia time of 20 hours].[12] The KDRI can give a sense of the increased risk of allograft failure or death associated with the use of a particular organ. For example, a KDRI of 1.22 means that the donor organ confers a 22% higher risk of allograft failure than the ideal reference donor (Fig. 1).

Strengths and Limitations

The KDRI provides a continuous score that estimates allograft outcomes. There is some doubt about its predictive power in certain donor subgroups. To test the discriminatory power of the KDRI model, the data set was split in half 5 separate times, and a *c* statistic was calculated for each split. A *c* statistic of 0.5 implies a prediction by chance, and a *c* statistic of 1.0 indicates a perfect prediction model. In the entire cohort, the average *c* statistic was 0.62, which indicated reasonable discriminatory power. In the extreme quartiles, the *c* statistic increased to 0.78, and in the middle 2 quartiles, it decreased to 0.58.[12] This suggests that the KDRI successfully predicts the extreme categories of allograft failure risk but does not easily distinguish donors from the middle ranges. Nonetheless, the KDRI can provide transplant candidates and their physicians with important information about accepting higher risk organs, and the risk can be balanced against the risk of remaining on the waiting list. This can lead to the acceptance of high-risk organs with adequate understanding and acceptance of the risk.

Future of Kidney Allocation

Using a model similar to the KDRI, OPTN/UNOS is considering a change to the kidney allocation system based on kidney characteristics.[13] The current system assigns ECD kidneys first to candidates willing to accept them. Kidneys from non-ECD donors are assigned to the waiting list as standard criteria donor

TABLE 1. Donor Characteristics Used in the KDPI

Donor Characteristics	Hazard Ratio	95% CI	*P* Value
Age			
Age − 40 years (applies to patients of all ages)	1.013	1.011-1.015	<0.001
Age − 18 years (applies to patients < 18 years old)	0.98	0.97-0.99	<0.001
Age − 50 years (applies to patients > 50 years old)	1.011	1.005-1.016	<0.001
Race: African American versus white	1.20	1.13-1.27	<0.001
Hypertensive	1.13	1.08-1.19	<0.001
Diabetic	1.14	1.04-1.24	<0.001
Creatinine			
SCR − 1 mg/dL (applies to all SCR values)	1.25	1.17-1.33	<0.001
SCR − 1.5 mg/dL (applies to SCR values > 1.5 mg/dL only)	0.81	0.74-0.89	<0.001
CVA as COD	1.09	1.04-1.14	<0.001
Height (per 10-cm increase)	0.96	0.94-0.97	<0.001
Weight (per 5-kg increase below 80 kg)	0.98	0.97-0.99	<0.001
DCD	1.14	1.02-1.28	0.02
HCV	1.27	1.13-1.43	<0.001

NOTE: The KDPI is derived from the KDRI developed by Rao et al.[12] and assumes an average transplant (ie, 2 mismatches at the HLA-B locus, 1 mismatch at the HLA-DR locus, 20 hours of cold ischemia, and not an en bloc or double transplant). It is calculated as follows:

$$\begin{aligned}\text{KDPI} = \exp\{&-0.0194 \times \text{I (Age} < 18 \text{ years)} \times (\text{Age} - 18 \text{ years}) + 0.0128 \times (\text{Age} - 40 \text{ years}) + 0.0107 \\ &\times \text{I (Age} > 50 \text{ years)} + 0.179 \times \text{I (Race = African American)} + 0.126 \times \text{I (Hypertensive)} + 0.130 \times \text{I (Diabetic)} \\ &+ 0.220 \times (\text{SCR} - 1 \text{ mg/dL}) - 0.209 \times \text{I (SCR} > 1.5 \text{ mg/dL)} \times (\text{SCR} - 1.5 \text{ mg/dL}) \\ &+ 0.0881 \times \text{I (COD = CVA)} - 0.0464 \times [(\text{Height} - 170 \text{ cm})/10] - 0.0199 \times \text{I (Weight} < 80 \text{ kg)} \\ &\times [(\text{Weight} - 80 \text{ kg})/5] + 0.133 \times \text{I (DCD)} + 0.240 \times \text{I (HCV)} - 0.0766\}\end{aligned}$$

where *I* is equal to 1 if the condition is true and *I* is equal to 0 if the condition is false.

kidneys. The proposed system will generate a kidney donor profile index (KDPI) score based only on donor characteristics (Table 1). Donor kidneys with the lowest KDPI score, which represents the longest predicted survival time, would be assigned to candidates with the longest estimated posttransplant survival. Kidneys with a KDPI score $\leq$ 20% would be offered first to candidates with the longest 20% estimated posttransplant survival and then to the pool of remaining candidates.

The KDPI is based on an average- or median-quality donor and not on an ideal reference donor as the original KDRI is.[12] Using an average donor in the KDPI score allows clinicians to estimate allograft survival in comparison with that of general kidney donors rather than a reference donor. This score provides a more applicable risk estimate that is based on current donor characteristics and not on the characteristics of a reference donor based on data from 1995 to 2005. However, if the reference donor population is updated annually, the KDPI value from year to year may not be the same for donors with similar risks of allograft failure.

The proposed change to the OPTN/UNOS allocation system (ie, a transition from the ECD criteria to the KDPI) would address the continued shortage of donor kidneys. The goal is to decrease the discard rates of marginal kidneys; this would increase kidney availability. Although the KDPI has marginal predictive power in the middle quartiles, the highest and lowest quartiles have been shown to be highly predictive of kidney transplant outcomes, especially in comparison with the ECD criteria. The use of donor risk indices in kidney transplantation has led to increasing interest in a similar method of evaluating donor factors to predict allograft survival in liver transplantation.

DONOR RISK INDICES IN LIVER TRANSPLANTATION

Importance of Donor Factors

Over the last 20 years, survival after liver transplantation has steadily improved.[14] However, because of the wide gap between donor organ availability and patients in need of transplantation, the use of marginal, high-risk or ECD organs has increased.[15] Although priority in liver allocation is based on the Model for End-Stage Liver Disease (MELD) score, donor-recipient matching occurs at the time of organ procurement and transplantation, and substantial selection is involved in accepting an organ.[16] The identification of donor-related factors that portend poor posttransplant outcomes and analyses that can guide the use of organs according to donor characteristics have become increasingly important,[17] especially because donor characteristics and medical management vary by region and organ procurement

TABLE 2. LDRI

Donor Characteristics	Hazard Ratio	95% CI	*P* Value
Age			
<40 years	1		
40-49 years	1.17	1.08-1.26	<0.001
50-59 years	1.32	1.21-1.43	<0.001
60-69 years	1.53	1.39-1.68	<0.001
>70 years	1.65	1.46-1.87	<0.001
Race: African American versus white	1.19	1.10-1.29	<0.001
Height (per 10-cm decrease)	1.07	1.04-1.09	<0.001
CVA as COD	1.16	1.08-1.24	<0.001
Other COD	1.2	1.03-1.40	0.02
DCD	1.51	1.19-1.91	<0.001
Partial/split liver	1.52	1.27-1.83	<0.001

NOTE: This table is adapted from Feng et al.[19] Data from the Scientific Registry of Transplant Recipients for adult deceased donor liver transplants (1998-2002) were used to identify donor factors associated with allograft failure after adjustments for recipient and transplant factors. The final LDRI model also includes regional and national sharing and the cold ischemia time. It is calculated as follows:

$$\begin{aligned}\text{LDRI} = \exp\{&(0.154 \text{ if } 40 \text{ years} \le \text{Age} < 50 \text{ years}) + (0.274 \text{ if } 50 \text{ years} \le \text{Age} < 60 \text{ years})\\ &+ (0.424 \text{ if } 60 \text{ years} \le \text{Age} < 70 \text{ years}) + (0.501 \text{ if } 70 \text{ years} \le \text{Age}) + (0.079 \text{ if COD} = \text{Anoxia})\\ &+ (0.145 \text{ if COD} = \text{CVA}) + (0.184 \text{ if COD} = \text{Other}) + (0.176 \text{ if Race} = \text{African American})\\ &+ (0.126 \text{ if Race} = \text{Other}) + (0.411 \text{ if DCD}) + (0.422 \text{ if Partial/Split}) + [0.066(170 - \text{Height})/10]\\ &+ (0.105 \text{ if Regional Share}) + (0.244 \text{ if National Share}) + (0.010 \times \text{Cold Ischemia Time})\}\end{aligned}$$

organization and may affect posttransplant outcomes.[18]

The most important donor factor is age, which has repeatedly been shown to be a significant predictor of allograft failure and posttransplant death.[17,19-22] This is especially true for patients undergoing transplantation for HCV; outcomes are significantly worse for patients with HCV who receive livers from older donors. Less is understood about the effects of older donor allografts, especially with respect to long-term outcomes, in non-HCV recipients. The type of donor is also important; the use of DCD livers is associated with an increased risk of posttransplant allograft failure.[23,24]

Several mathematical models have been proposed to identify predictors of allograft and patient survival after liver transplantation. The MELD score is an excellent predictor of wait-list mortality but a suboptimal predictor of posttransplant allograft and patient survival because of donor, recipient, and transplant characteristics and unpredictable posttransplant events (eg, patient compliance, allograft primary nonfunction, and hepatic artery thrombosis). Objective parameters that quantify the risk associated with donor organs are actively being sought.

LDRI

Derivation

In their seminal article, Feng et al.[19] discuss the concept of the LDRI. They used data from adult deceased donor liver transplants in the United States (1998-2002) to identify factors associated with allograft failure. After adjustments for recipient and transplant factors that might affect allograft failure, a set of donor characteristics that were significant in multivariate modeling was derived. The original report identified 7 donor characteristics that were significantly associated with liver allograft failure (Table 2). The final LDRI model also included regional and national sharing and the cold ischemia time. Donor age $\ge$ 60 years, DCD livers, and partial/split livers were associated with the highest risk of allograft failure. Livers from African American donors were associated with a 19% higher risk of allograft failure in comparison with livers from white donors. With a reference donor (age < 40 years, death due to trauma, white race, cold ischemia time $\le$ 8 hours, height of 170 cm, local organ procurement, and whole non-DCD organ), several combinations of donor characteristics were examined. Allograft survival rates correlated with increasing LDRI. Allograft survival was highest with the reference donor [LDRI $\le$ 1 (20% of transplants)]; the 1-year survival rate was 87.6% (86.6%-88.7%), and the 3-year survival rate was 81.2% (79.9%-82.6%). The 1-year survival rate for organs with an LDRI $\ge$ 2 (6% of transplants) was 71.4% (68.8%-74.1%), and the 3-year survival rate was 60.0% (56.9%-63.2%). The authors also reported that allografts with higher LDRIs were likely to be used for recipients with low disease severity (MELD score = 10-14).

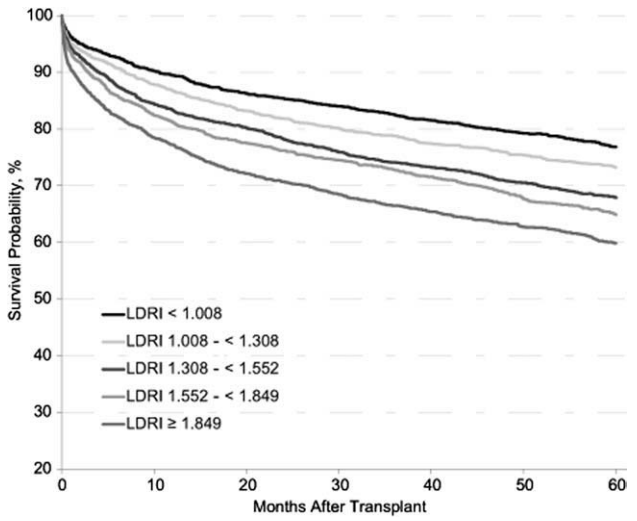

Figure 2. Probability of survival after liver transplantation for transplant recipients (2005-2006) according to the LDRI values. Only first transplants were included. Multiorgan transplants were excluded, and no adjustments were made for recipient and other donor factors.

Strengths

The immediate impact of the LDRI was an appreciation of the importance of donor factors and their influence on survival (Fig. 2). In an analysis of transplant recipients (2005-2006), the 3-year survival rates ranged from 66% to 83% according to the LDRI. The LDRI provided the transplant community a common language (akin to the MELD score) for describing donor organ characteristics. It allowed transplant teams to formally consider variables in donor-recipient matching that previously were considered intuitively at the time of organ procurement and transplantation. It allowed a formal assessment of the risks posed by a particular allograft and the potential risk of death if an organ were declined.[19] Furthermore, it allowed the standardized assessment of transplant practices. Subsequent analyses confirmed the importance of the LDRI.[25,26] Maluf et al.[25] examined the use of ECD livers (LDRI $\geq$ 1.7) that were transplanted between 2002 and 2005. These high-risk donor livers were associated with a significant increase in the relative risk of allograft failure in each MELD category.

Limitations

Although the LDRI serves an important role in assessing donor quality, much work remains to be done to validate and optimize it. First, the LDRI was derived from data available in the pre-MELD era. Because the MELD-based allocation system represented a fundamental change in the practice of liver transplantation, the LDRI should be examined with a modern, independent data set. Because the characteristics of currently wait-listed candidates differ from the characteristics of patients who underwent transplantation in the previous decade, changes in the significance and relative weighting of the included variables are likely. Even for the highly vetted MELD score, refitting the score coefficients with an updated data set produced several changes in the relative importance of the variables.[27] Second, most of the predictive ability of the LDRI is derived from the donor's age, which single-handedly explains a significant amount of the variability in posttransplant outcomes.[25,28]

Third, certain variables included in the model primarily because of statistical significance during multivariate modeling lack biological plausibility. Donor race should not be construed as an indicator of donor quality.[17] Several factors confound the association between donor race and allograft failure, including the transplant center, the transplantation of donor organs too small for the recipient body size, and the transplantation of hepatitis B core–positive organs into hepatitis B–naive recipients. According to an updated data set (January 2003 to December 2005), the risk of allograft failure associated with African American donor race was lower and was no longer significant once the transplant center was considered. In the original LDRI, there was a 19% elevated risk associated with African American donor organs; after appropriate adjustments, the elevated risk was only 5% and was no longer significant. Furthermore, an interaction between donor race and recipient race was observed, with variable rates of allograft failure in separate donor-recipient pairs. Hence, the assignment of a singular risk for all donor-recipient pairs by race has been shown to be misleading.[17,29]

Fourth, other variables such as the COD and regional or national sharing do not have a consistently negative impact on allograft survival.[17,30] Other donor variables not included in the LDRI have been identified as important predictors of allograft failure.[31] The LDRI was derived through the retrospective use of SRTR data primarily collected to study recipient characteristics, and it is limited in the number of variables and by the extent of the reporting of the collected data.[32] Hence, unknown effects of missing variables (eg, macrosteatosis on donor biopsy) have been addressed by several authors.[17,28]

Finally, the derivation of the LDRI involved the consideration of approximately 60 variables; the inclusion or exclusion of variables was driven by statistical modeling. This approach makes the analysis of important interactions more difficult and may inadvertently ignore collinearity among variables explaining the same effect. Clearly, much work is needed to refine and validate measures to objectively gauge the quality of donated organs. Using donor factors in isolation may give the LDRI poor predictive value.[33] The effect of a high-risk donor is likely modified by important recipient characteristics such as the HCV status.[25,34]

Application of the LDRI

An indirect benefit of the better assessment of donor quality with the LDRI (and the assessment of recipient mortality risk with the MELD score) is the ability to

fine-tune the distribution of a scarce resource. Furthermore, practices that appear sound but may instead be detrimental to overall posttransplant outcomes can be examined.[35,36] The LDRI has allowed the transplant community to further assess the organ allocation process and refine it to serve the needs of liver transplant patients.

LDRI and HCV Recipients

Donor age is one of the most significant drivers of the LDRI, and it is evident that HCV recurrence and subsequent allograft failure are more likely with older donor liver allografts.[28] Maluf et al.[25] showed that as the LDRI increases, the rates of allograft failure and death increase more in recipients with HCV versus non-HCV recipients. This difference persists even after adjustments for several recipient factors, including the MELD score. In this study, much of the effect of the LDRI (70%) was explained by donor age. Several reports have examined the interaction between donor age and HCV status. Schaubel et al.[34] showed that for non-HCV recipients, the hazard ratio for allograft failure with a donor age $\geq$ 60 years was 1.44, and it increased to 2.03 if the recipient was HCV-positive; this was a greater than 2-fold increase in the posttransplant mortality risk. Again, the LDRI led to a formal analysis of the effects of donor characteristics (namely donor age and its negative implications) and supported a global practice change toward transplanting organs from younger donors into recipients with HCV.

LDRI and Its Economic Impact

The use of organs with high LDRIs is associated with increased hospital costs that are independent of recipient risk factors.[37] Across each MELD score category, resource utilization and the hospital length of stay increase with increasing LDRI. In addition, the combination of a high LDRI and a high MELD score is associated with the highest cost, albeit with acceptable posttransplant survival.

LDRI and the Use of High-Risk Organs

Volk et al.[38] examined donor-recipient matching in the MELD era. The overall quality of organs (as quantified by the LDRI) has decreased, and higher risk organs are being transplanted into less urgent candidates (in the MELD era); this has led to worse outcomes for these candidates and reduced posttransplant survival in recent years among patients with low MELD scores. Similarly, Schaubel et al.[39] showed that high-LDRI organs were more often transplanted into recipients with lower MELD scores and vice versa. The lowest MELD category recipients (score = 6-8) who received high-LDRI organs experienced significantly higher mortality (hazard ratio = 3.70, $P < 0.01$) than they would have if they had waited for a lower LDRI organ. This led to a paradigm shift; high-risk organs are less frequently transplanted into recipients with low MELD scores. Others have confirmed the detrimental effect of transplanting ECD organs (as defined by an elevated LDRI) into recipients with low MELD scores (<15).[40,41] An alternative conclusion is that high-risk organs should be transplanted into candidates who face a high mortality risk without transplantation and, therefore, can benefit substantially from transplantation.[28]

Geographic Disparity

The objective characterization of donor risk allows the examination of geographic disparities in donor quality. Regions with the longest wait times tend to transplant organs with higher LDRIs. Differences in donor quality among the 11 OPTN/UNOS regions have led to disparate rates of allograft survival.[42] Recently, even center-based differences in posttransplant outcomes have been examined as a function of donor quality. Despite adjustments for geography and patient characteristics (including disease severity), the quality of donor organs differs between centers (LDRI = 1.74-2.37). Posttransplant mortality tends to be higher at centers using higher risk organs (hazard ratio = 1.10 per 0.1 increase in the mean LDRI), and this implies that outcomes for liver transplant candidates may be variable between centers.[43] Conversely, a separate analysis concluded that patient survival and allograft survival were better at high-volume centers, despite the use of high-risk donors (higher LDRI).[44,45] Regardless, a center effect on allograft failure is apparent, even after adjustments for the LDRI.[46] Hence, factors other than those included in the LDRI may play a role.

Donor-Recipient Matching

Isolating donor characteristics from the multitude of factors that may influence posttransplant outcomes is difficult. Several authors have attempted to identify predictors of allograft failure and objectively characterize donor-recipient matching. One example is a model derived from 4 donor characteristics (age, cold ischemia time, sex, and race/ethnicity) and 9 recipient characteristics (age, body mass index, MELD score, OPTN/UNOS priority status, sex, race/ethnicity, diabetes mellitus, cause of liver disease, and serum albumin).[21] Separate models were developed to predict posttransplant survival in patients with HCV and in patients without HCV. Older donors (age > 75 years) and split liver recipients were excluded in contrast to the LDRI. More than 60 variables were considered. The risk of death was substantially different for high-risk recipients and low-risk recipients; 1-year survival varied from 53% to 96% according to a combination of donor and recipient factors. Within the data set, the importance of donor characteristics (age, race, sex, and cold ischemia time), designated the score of liver donor (SOLD), was directly related to posttransplant survival; the higher the score, the

lower the survival.[21] However, the score was derived primarily from the pre-MELD era and considered variables that may lack biological plausibility (eg, donor race). Furthermore, the performance characteristics of the model (eg, *c* statistic) were not provided.

Similarly, Rana et al.[33] identified 13 recipient factors, 4 donor factors, and 2 operative factors (warm and cold ischemia times) as significant predictors of recipient mortality 3 months after transplantation, using MELD era data and including retransplants. Using 18 risk factors (excluding the warm ischemia time), the survival outcomes following liver transplantation (SOFT) score successfully predicted 3-month recipient survival. The SOFT score included the MELD score at the time of transplantation (categorized as >30 or ≤30). In their analysis of predicting 3-month mortality after liver transplantation, the concordance statistic was 0.63 for the MELD score and 0.70 for the SOFT score. In comparison, the MELD score *c* statistic was greater than 0.85 for predicting wait-list mortality.[27] Donor race was not a significant predictor in this study. Concerns similar to those outlined previously and complex statistical modeling limit its widespread application. Furthermore, longer time periods are needed to judge successful transplants; 3-month mortality estimates may be highly influenced by perioperative factors, which may be indirectly related to transplant center characteristics.

Retransplant Donor Risk Index

The original LDRI does not include patients undergoing retransplantation. Northup et al.[26] examined all retransplants performed in the United States since 2002. The LDRI was a significant predictor of overall mortality [hazard ratio = 2.2 (1.63-2.94)]. Adding the cause of allograft failure to the LDRI increased the risk of mortality [hazard ratio = 2.49 (1.89-3.27)]. Surprisingly, in patients with HCV as a component of allograft failure, the use of a high-risk organ did not independently influence overall survival.[26] This finding, if confirmed, would represent a significant shift in our understanding of the mortality risk after retransplantation.

Concordance Between the LDRI and the KDRI

The *c* statistic for concordance between the LDRI and the KDRI is 0.80. This is not surprising because the 2 indices use similar factors (Tables 1 and 2). Both indices include donor demographics (age and African American race), DCD, donor size (height and weight in the KDRI and height and partial/split liver in the LDRI), and stroke as the cause of donor death. These factors all work in the same direction in both indices. Therefore, in a recent analysis, the *c* statistic for the KDRI for predicting outcomes after liver transplantation was similar to the *c* statistic for the LDRI (*c* statistic = 0.57).[47]

The KDRI differs from the LDRI in that it incorporates more kidney-specific comorbid conditions that can affect kidney function (donor diabetes and hypertension) and the intended recipient (donor HCV serostatus). The KDRI also incorporates donor kidney function through the measurement of the donor SCR level. Therefore, OPTN/UNOS is considering the use of the KDRI in a future kidney allocation system.[13] Whether the liver transplant community will use the LDRI in a future allocation system remains to be seen.

CONCLUSION

The development of mathematical models that predict the risk of allograft failure took a giant leap after the introduction of the LDRI and the KDRI. Despite their limitations, these models allow us to quantify and qualify the risks associated with the use of higher risk donor organs and allow the standardized assessment of practices across the transplant community. However, the models can be improved. A rigorously vetted donor information database should be created, and data should be collected prospectively to quantify the risk associated with high-risk donors.[32] This would provide an objective element to donor-recipient matching that occurs in the middle of the night and help to improve posttransplant outcomes.[14] However, variables based on clinical judgment and not simply statistical significance should be used; this would be possible in any large data set. A careful evaluation is needed before a characteristic is defined as high-risk to forestall a slippery slope on which organs with certain characteristics (eg, African American donor) are considered inferior, are transplanted into high-risk recipients, and are eventually associated with poor outcomes; this would culminate in a vicious cycle that would be hard to disprove in future analyses. Neither the KDRI nor the LDRI accounts for the donor risk of transmitting viral infections, such as human immunodeficiency virus, hepatitis B virus, and HCV, as determined by the Centers for Disease Control and Prevention criteria for high-risk donors.[48,49] The allograft survival of organs from donors with a higher risk for transmitting infections has been found to be better than the survival of high-risk organs as determined by the KDRI.[50] However, the largest benefit derived from indices of donor risk is the opportunity for better discussion with patients and informed deliberation between physicians and transplant candidates about the importance of factors that affect posttransplant results.[51] Providing patients with donor risk data should be an important part of informed consent. Minimally, this means providing the most accurate information about the relative risks of accepting a higher risk organ and remaining on a waiting list. Such information can help to guide decisions by physicians and transplant candidates about donor acceptance criteria. In turn, this will facilitate the expeditious placement of high-risk organs and maximize organ utilization.

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REFERENCES

1. Miranda B, Fernández Lucas M, de Felipe C, Naya M, González-Posada JM, Matesanz R. Organ donation in Spain. Nephrol Dial Transplant 1999;14(suppl 3):15-21.
2. Rao KV, Kasiske BL, Odlund MD, Ney AL, Andersen RC. Influence of cadaver donor age on posttransplant renal function and graft outcome. Transplantation 1990;49: 91-95.
3. Terasaki PI, Gjertson DW, Cecka JM, Takemoto S, Cho YW. Significance of the donor age effect on kidney transplants. Clin Transplant 1997;11(pt 1):366-372.
4. Rosengard BR, Feng S, Alfrey EJ, Zaroff JG, Emond JC, Henry ML, et al. Report of the Crystal City meeting to maximize the use of organs recovered from the cadaver donor. Am J Transplant 2002;2:701-711.
5. Port FK, Bragg-Gresham JL, Metzger RA, Dykstra DM, Gillespie BW, Young EW, et al. Donor characteristics associated with reduced graft survival: an approach to expanding the pool of kidney donors. Transplantation 2002;74:1281-1286.
6. Ojo AO, Wolfe RA, Leichtman AB, Dickinson DM, Port FK, Young EW. A practical approach to evaluate the potential donor pool and trends in cadaveric kidney donation. Transplantation 1999;67:548-556.
7. Sung RS, Guidinger MK, Leichtman AB, Lake C, Metzger RA, Port FK, Merion RM. Impact of the expanded criteria donor allocation system on candidates for and recipients of expanded criteria donor kidneys. Transplantation 2007;84:1138-1144.
8. Merion RM, Ashby VB, Wolfe RA, Distant DA, Hulbert-Shearon TE, Metzger RA, et al. Deceased-donor characteristics and the survival benefit of kidney transplantation. JAMA 2005;294:2726-2733.
9. Nyberg SL, Matas AJ, Rogers M, Harmsen WS, Velosa JA, Larson TS, et al. Donor scoring system for cadaveric renal transplantation. Am J Transplant 2001;1:162-170.
10. Nyberg SL, Matas AJ, Kremers WK, Thostenson JD, Larson TS, Prieto M, et al. Improved scoring system to assess adult donors for cadaver renal transplantation. Am J Transplant 2003;3:715-721.
11. Schold JD, Kaplan B, Baliga RS, Meier-Kriesche HU. The broad spectrum of quality in deceased donor kidneys. Am J Transplant 2005;5(pt 1):757-765.
12. Rao PS, Schaubel DE, Guidinger MK, Andreoni KA, Wolfe RA, Merion RM, et al. A comprehensive risk quantification score for deceased donor kidneys: the kidney donor risk index. Transplantation 2009;88:231-236.
13. Organ Procurement and Transplantation Network. Concepts for kidney allocation. http://optn.transplant.hrsa.gov/SharedContentDocuments/KidneyConceptDocument.PDF. Accessed January 2012.
14. Thuluvath PJ, Guidinger MK, Fung JJ, Johnson LB, Rayhill SC, Pelletier SJ. Liver transplantation in the United States, 1999-2008. Am J Transplant 2010;10(pt 2):1003-1019.
15. Gordon Burroughs S, Busuttil RW. Optimal utilization of extended hepatic grafts. Surg Today 2009;39:746-751.
16. Asrani SK, Kim WR. Organ allocation for chronic liver disease: Model for End-Stage Liver Disease and beyond. Curr Opin Gastroenterol 2010;26:209-213.
17. Asrani SK, Lim YS, Therneau TM, Pedersen RA, Heimbach J, Kim WR. Donor race does not predict graft failure after liver transplantation. Gastroenterology 2010; 138:2341-2347.
18. Selck FW, Grossman EB, Ratner LE, Renz JF. Utilization, outcomes, and retransplantation of liver allografts from donation after cardiac death: implications for further expansion of the deceased-donor pool. Ann Surg 2008; 248:599-607.
19. Feng S, Goodrich NP, Bragg-Gresham JL, Dykstra DM, Punch JD, DebRoy MA, et al. Characteristics associated with liver graft failure: the concept of a donor risk index. Am J Transplant 2006;6:783-790.
20. Halldorson JB, Bakthavatsalam R, Fix O, Reyes JD, Perkins JD. D-MELD, a simple predictor of post liver transplant mortality for optimization of donor/recipient matching. Am J Transplant 2009;9:318-326.
21. Ioannou GN. Development and validation of a model predicting graft survival after liver transplantation. Liver Transpl 2006;12:1594-1606.
22. Cuende N, Miranda B, Cañón JF, Garrido G, Matesanz R. Donor characteristics associated with liver graft survival. Transplantation 2005;79:1445-1452.
23. Mateo R, Cho Y, Singh G, Stapfer M, Donovan J, Kahn J, et al. Risk factors for graft survival after liver transplantation from donation after cardiac death donors: an analysis of OPTN/UNOS data. Am J Transplant 2006;6:791-796.
24. Reich DJ, Hong JC. Current status of donation after cardiac death liver transplantation. Curr Opin Organ Transplant 2010;15:316-321.
25. Maluf DG, Edwards EB, Stravitz RT, Kauffman HM. Impact of the donor risk index on the outcome of hepatitis C virus-positive liver transplant recipients. Liver Transpl 2009;15:592-599.
26. Northup PG, Pruett TL, Kashmer DM, Argo CK, Berg CL, Schmitt TM. Donor factors predicting recipient survival after liver retransplantation: the retransplant donor risk index. Am J Transplant 2007;7:1984-1988.
27. Leise MD, Kim WR, Kremers WK, Larson JJ, Benson JT, Therneau TM. A revised Model for End-Stage Liver Disease optimizes prediction of mortality among patients awaiting liver transplantation. Gastroenterology 2011; 140:1952-1960.
28. Feng S. Increased donor risk: who should bear the burden? Liver Transpl 2009;15:570-573.
29. Eckhoff DE, McGuire BM, Young CJ, Sellers MT, Frenette LR, Hudson SL, et al. Race: a critical factor in organ donation, patient referral and selection, and orthotopic liver transplantation? Liver Transpl Surg 1998;4: 499-505.
30. Mangus RS, Fridell JA, Vianna RM, Kwo PY, Chestovich P, Milgrom ML, et al. No difference in clinical transplant outcomes for local and imported liver allografts. Liver Transpl 2009;15:640-647.
31. Nafidi O, Marleau D, Roy A, Bilodeau M. Identification of new donor variables associated with graft survival in a single-center liver transplant cohort. Liver Transpl 2010; 16:1393-1399.
32. Renz JF. A critical analysis of liver allograft utilization from the US deceased donor pool. Liver Transpl 2010; 16:543-547.
33. Rana A, Hardy MA, Halazun KJ, Woodland DC, Ratner LE, Samstein B, et al. Survival outcomes following liver transplantation (SOFT) score: a novel method to predict patient survival following liver transplantation. Am J Transplant 2008;8:2537-2546.
34. Schaubel DE, Guidinger MK, Biggins SW, Kalbfleisch JD, Pomfret EA, Sharma P, Merion RM. Survival benefit-based deceased-donor liver allocation. Am J Transplant 2009;9(pt 2):970-981.
35. Brown RS Jr, Lake JR. The survival impact of liver transplantation in the MELD era, and the future for organ allocation and distribution. Am J Transplant 2005;5: 203-204.
36. Hameed B, Lake JR. Using higher risk organs for liver transplantation: in whom and at what price? Gastroenterology 2008;135:1452-1454.
37. Axelrod DA, Schnitzler M, Salvalaggio PR, Swindle J, Abecassis MM. The economic impact of the utilization of

liver allografts with high donor risk index. Am J Transplant 2007;7:990-997.
38. Volk ML, Lok AS, Pelletier SJ, Ubel PA, Hayward RA. Impact of the Model for End-Stage Liver Disease allocation policy on the use of high-risk organs for liver transplantation. Gastroenterology 2008;135:1568-1574.
39. Schaubel DE, Sima CS, Goodrich NP, Feng S, Merion RM. The survival benefit of deceased donor liver transplantation as a function of candidate disease severity and donor quality. Am J Transplant 2008;8:419-425.
40. Bonney GK, Aldersley MA, Asthana S, Toogood GJ, Pollard SG, Lodge JP, Prasad KR. Donor risk index and MELD interactions in predicting long-term graft survival: a single-centre experience. Transplantation 2009;87:1858-1863.
41. Maluf DG, Edwards EB, Kauffman HM. Utilization of extended donor criteria liver allograft: is the elevated risk of failure independent of the Model for End-Stage Liver Disease score of the recipient? Transplantation 2006;82: 1653-1657.
42. Asrani SK, Kim WR, Kamath PS. Race and receipt of liver transplantation: location matters. Liver Transpl 2010;16: 1009-1012.
43. Volk ML, Reichert HA, Lok AS, Hayward RA. Variation in organ quality between liver transplant centers. Am J Transplant 2011;11:958-964.
44. Ozhathil DK, Li Y, Smith JK, Tseng JF, Saidi RF, Bozorgzadeh A, Shah SA. Effect of centre volume and high donor risk index on liver allograft survival. HPB (Oxford) 2011;13:447-453.
45. Ozhathil DK, Li YF, Smith JK, Tseng JF, Saidi RF, Bozorgzadeh A, Shah SA. Impact of center volume on outcomes of increased-risk liver transplants. Liver Transpl 2011;17:1191-1199.
46. Asrani SK, Pedersen RA, Thabut G, Kremers WK, Therneau TM, Heimbach JK, Kim WR. Impact of center on graft failure after liver transplantation [abstract]. Liver Transpl 2010;16(suppl 1):S97.
47. Stewart DE, Edwards LB, Metzger RA. Is the kidney donor risk index (KDRI) a useful predictor of graft survival for non-renal organs? [abstract]. Am J Transplant 2011; 11(suppl 2):169.
48. Reese PP, Halpern SD, Asch DA, Bloom R, Nathan H, Hasz R, et al. Longer-term outcomes after kidney transplantation from seronegative deceased donors at increased risk for blood-borne viral infection. Transplantation 2011;91:1211-1217.
49. Jensen PA, Lambert LA, Iademarco MF, Ridzon R. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings. 2005. Centers for Disease Control. MMWR Recomm Rep 2005;54(RR-17):1–141.
50. Reese PP, Feldman HI, Asch DA, Halpern SD, Blumberg EA, Thomasson A, et al. Transplantation of kidneys from donors at increased risk for blood-borne viral infection: recipient outcomes and patterns of organ use. Am J Transplant 2009;9:2338-2345.
51. Freeman RB, Jamieson N, Schaubel DE, Porte RJ, Villamil FG. Who should get a liver graft? J Hepatol 2009;50: 664-673.