Donor and Recipient Effects on Graft and Patient Survival

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The careful selection of donor organs and recipients of liver transplantation (LT) is becoming increasingly important with the rising use of expanded criteria donors in an aging recipient population. Understanding the complex interplay of donor and recipient risk factors is essential to improving outcomes.

Deceased Donor Effects

Donor Risk Index. The donor risk index attempts to quantify the recipient risk of graft failure associated with donor characteristics at the time of the organ offer: a donor age greater 40 years, donation after cardiac death, split grafts, African American race, shorter height, cerebrovascular accident, and other causes of brain death (Table 1).[1] However, without clear evidence of improving outcomes, its clinical utility has been questioned.[2]

Donor Age. Multiple studies have illustrated the negative impact of older donors. Although there is no universally accepted age limit, one study found that the use of donors older than 70 years led to a markedly worse 5-year patient survival rate of 47%.[3] A donor age older than 40 years for recipients with hepatitis C virus (HCV) has been found to be a strong predictor of graft loss and death and is associated with the development of fibrosing cholestatic hepatitis.[4-6]

Hepatic Steatosis. Moderate (30%-60%) and massive (>60%) macrovesicular steatosis has been associated with early graft dysfunction and primary nonfunction (Fig. 1). The impact of severe macrovesicular steatosis on graft survival may be greater than the impact of other donor factors, including the donor risk index. In contrast, donor microvesicular steatosis has been linked to poor early graft function when it is severe, but it does not seem to affect overall graft or patient survival.[7]

Infections and High-Risk Donors According to the Centers for Disease Control and Prevention. Although donors with systemic infections, a history of cardiopulmonary resuscitation, and inotropic medications are independent predictors of donor graft infection, there is no evidence of an effect on recipient survival.[8] Although rare (0.96%),[9] donor-derived disease transmission (e.g., HCV and human immunodeficiency virus) is a recognized contributor to morbidity and mortality.[10]

Cold Ischemia Time. Cold preservation can affect graft and patient survival if it is more than 12 hours long, especially with other negative variables.[11] A prolonged ischemic time has been associated with increased reperfusion injury, primary nonfunction, and the need for retransplantation.[11,12]

Deceased Cardiac Donors. In an effort to expand the US donor pool, the use of donation after cardiac death organs has increased from <1% to more than 6% in the past decade. Reported outcomes vary dramatically between transplant centers because of variations in donor characteristics and surgical techniques. However, the use of donation after cardiac death organs has been associated with higher rates of primary nonfunction, nonanastomotic biliary strictures, resource utilization, renal dysfunction, and graft failure in comparison with donation after brain death organs.[13-15]

Sex/Race/Genetics. A multivariate analysis found that the transplantation of organs from female donors into male recipients led to lower 2-year graft survival rates in comparison with other sex combinations.[16] African American recipients

Abbreviations: HCV, hepatitis C virus; LT, liver transplantation.

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TABLE 1: Adjusted Donor Factors Significantly Associated With Liver Allograft Failure: Factors of the Donor Risk Index

Donor Parameter	Relative Risk	95% Confidence Interval	*P* Value
Age			
<40 years	1.00		
40-49 years	1.17	1.08-1.26	0.0002
50-59 years	1.32	1.21-1.43	<0.0001
60-69 years	1.53	1.39-1.68	<0.0001
>70 years	1.65	1.46-1.87	<0.0001
African American race versus white race	1.19	1.10-1.29	<0.0001
Donor height (per 10-cm decrease)	1.07	1.04-1.09	<0.0001
Cerebrovascular accident as cause of death	1.16	1.08-1.24	<0.0001
Donation after cardiac death	1.51	1.19-1.91	0.0006
Partial/split graft	1.52	1.27-1.83	<0.0001

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of grafts from Caucasian donors and Hispanic recipients of grafts from African American donors were also found to have higher rates of graft loss and mortality than Caucasian-matched pairs.[17] The pairing of African American donors with Hispanic recipients has significantly decreased graft loss and mortality in comparison with Caucasian-matched pairs. The effect of racial mismatch may be even more pronounced in HCV recipients, and perhaps this is related to interleukin-28B genotypes.[18,19] Additionally, certain donor toll-like receptor 4 gene polymorphisms have been associated with a higher rate of graft failure in all populations.[20]

Living Donors.

One multicenter study found that living donor recipients had an increased risk of biliary leaks, re-exploration, and vascular thrombosis.[21] However, once centers had performed more than 20 procedures, the rate of nonbiliary complications was similar to the rate with deceased donation.

TABLE 2: Recipient Factors: Cox Regression Analysis Models for Graft and Patient Survival

Variable	Graft Survival		Patient Survival	
	Hazard Ratio	95% Confidence Interval	Hazard Ratio	95% Confidence Interval
Etiology vs chronic cholestatic liver disease				
HCV	1.61	1.52-1.74	1.97	1.84-2.11
Alcoholic liver disease	1.28	1.2-1.69	1.64	1.52-1.77
Alcoholic liver disease + HCV	1.6	1.46-1.69	2.1	1.9-2.23
Nonalcoholic steatohepatitis	1.19	1.04-1.37	1.52	1.3-1.77
Chronic cholestatic	1.27	1.18-1.35	1.53	1.42-1.66
Hepatitis B virus	1.07	0.96-1.19	1.3	1.15-1.47
Hepatocellular carcinoma	1.67	1.56-1.78	2.15	1.99-2.32
Age increase (for every 10 years)	1.09	1.07-1.11	1.24	1.22-1.27
Female versus male	0.99	0.96-1.03	1.05	1.01-1.09
African American versus Caucasian	1.28	1.21-1.36	1.33	1.24-1.42
Ventilator support	1.85	1.67-2.05	1.63	1.44-1.84
Model for End-Stage Liver Disease score increase (for every 3 points)	1.03	1.03-10.4	1.05	1.04-1.06

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Recipient Effects

Models Predicting Post-LT Outcomes.

Although the Model for End-Stage Liver Disease score is a sensitive predictor of death on the LT wait list, its use for predicting post-LT outcomes is more limited. Other models, such as the Acute Physiology and Chronic Health Evaluation II score, the Charlson comorbidity index, and the Survival Outcomes Following Liver Transplantation score[22] have been used but not fully implemented.

Etiology of Liver Disease.

A recent analysis of United Network for Organ Sharing data for adult transplants from 1994 to 2009 revealed that in comparison with primary biliary cirrhosis, the 5-year graft and patient survival rates were similar for primary sclerosing cholangitis, nonalcoholic steatohepatitis, and hepatitis B. When compared to chronic

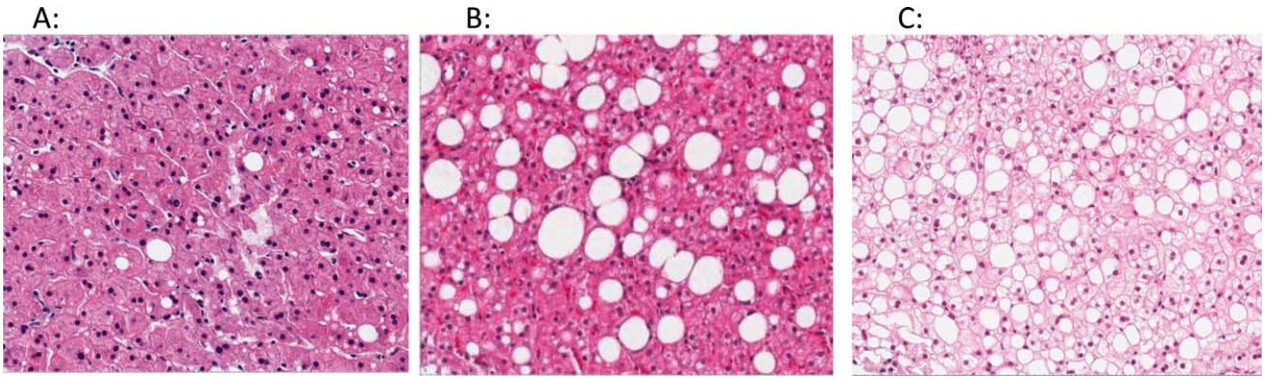

FIGURE 1. Examples of hepatic macrosteatosis (hematoxylin and eosin stains, ×10; photographs courtesy of A. Brad Farris, M.D.). (A) Mild steatosis, which is defined as <30% of hepatocytes affected (<5% in this example). (B) Moderate steatosis (30%-60%), which has been associated in some studies with increased primary nonfunction and graft loss (~33% in this example). (C) Severe steatosis, which is defined as >60% involvement (~90% in this example). This is considered a contraindication to an organ's use as a donor graft.

cholestatic liver disease. The graft and patient survival rates were worse for alcoholic cirrhosis and cryptogenic cirrhosis (hazard ratio = 1.3-1.6) and worst for HCV, alcohol and HCV combined, and hepatocellular carcinoma (hazard ratio = 1.3-2.3; Table 2).[23] Although recipients with nonalcoholic steatohepatitis appear to experience more post-LT cardiovascular events,[24] graft and patient survival remain comparable to those with other etiologies.[25] For recipients with HCV, independent predictors of progressive fibrosis and graft loss include female sex,[26] a recipient age > 50 years (especially with older grafts),[27] elevated pre-LT HCV RNA titers ($>1 \times 10^6$ vEq/mL)[28], acute rejection, and HCV/human immunodeficiency virus coinfection.[29]

Age. An increasing number of candidates older than 65 years are being referred for evaluation, and they are often denied because of other comorbid conditions. However, few studies (except in HCV-positive recipients) have systematically examined the outcomes of carefully selected older recipients with minimal extrahepatic comorbidities.[30]

Comorbid Conditions. The incorporation of renal function into the Model for End-Stage Liver Disease has in part increased the frequency of simultaneous liver-kidney transplants from 2.5% in 1994 to 10.3% in 2009.[23] Although simultaneous liver-kidney transplantation is controversial, recipients have improved survival and less post-LT renal failure in comparison with recipients of LT alone.[31] Although exclusion criteria for cardiovascular disease also vary between transplant centers, post-LT survival appears to be similar in patients with obstructive coronary artery disease and patients without obstructive coronary artery disease with current management strategies.[32]

Conclusions

Understanding donor and recipient risk factors for post-transplant outcomes is essential, even though the pairing of particular donor grafts with recipients is still an evolving science.

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