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Transplant for the Very Sick: No Limitations in Donor Quality?

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Abstract

When it comes to maximizing allograft function, the recipient is just as important as the liver graft itself. Whereas the "healthiest" of liver transplant candidates are likely to gain significant benefit from a liver graft of any quality, the sickest of candidates may still die despite transplantation with even an ideal liver. However, the very sick patients are precisely the ones who have the greatest need for liver transplantation—with any liver, regardless of quality—because they are most vulnerable to pretransplant death without one. How does one balance the urgent need for liver transplantation with optimization of the allograft's function and utility for the very sick patient?

Donor Quality and Posttransplant Outcomes

In order to begin to answer this question, we must first review the importance of liver donor quality to posttransplant outcomes independent of recipient characteristics. Over the last 2 decades, numerous donor factors have been associated with poor posttransplant outcomes, but several factors have emerged as dominant: older donor age, donation after cardiac death status (DCD), long cold ischemia time (CIT), and macrovesicular steatosis.[1] Beginning at the age of 50 years, "older" donor age has been associated with primary nonfunction (PNF),[2–5] hepatic artery thrombosis,[6] more severe ischemia/reperfusion injury,[7,8] biliary complications,[9,10] and mortality.[11–14] In a meta-analysis of 11 studies evaluating posttransplant outcomes with DCD livers, recipients of DCD livers experienced higher rates of ischemic cholangiopathy and other biliary complications, PNF, and death.[15] Similarly, long CIT, particularly over 8 hours, confers added risk for nonanastamotic biliary strictures[16] and graft loss.[11] Large droplet fat—or macrovesicular steatosis—accumulating in >60% of the allograft is widely considered prohibitive for transplantation because recipients of these livers experience unacceptably high rates of PNF, graft failure, and death.[17–21] That being said, even livers with 30%–60% macrovesicular steatosis are risky and should only be used in the absence of other dominant donor risk factors.[18,19]

Clearly, donor quality, particularly with respect to age, DCD status, CIT, and macrovesicular steatosis, plays a large role in the outcomes of the average liver transplant recipient. Not only do age, DCD status, CIT, and macrovesicular steatosis predict clinically relevant

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outcomes, but with the exception of CIT, they are all increasing in prevalence in the liver donor pool.[22] It is, therefore, all the more critical to understand in whom marginal-quality livers can effectively be transplanted.

The Relationship Between Donor Quality and the Recipient's Severity of Illness

Analyses of US national registry data have failed to demonstrate a statistical interaction between liver donor quality (as measured by the donor risk index [DRI], a composite donor quality metric[11]) and recipient disease severity (as measured by Model for End-Stage Liver Disease [MELD] score) on posttransplant mortality.[23] Despite the absence of a statistical interaction, however, there is undoubtedly a relationship between donor quality and recipient sickness with respect to posttransplant metrics. Figure 1 illustrates how a marginal-quality liver might disproportionately impact posttransplant outcomes in a "sick" versus a "healthy" patient. Regardless of the recipient's health, liver transplant surgery leads to an initial precipitous drop in physiologic reserve. A marginal-quality liver (represented by the solid lines) can lead to a larger drop. For a "healthy" patient—such as one who has a low MELD score, has few medical comorbidities, and/or is physically fit—transplantation with a marginal-quality liver may lead to a longer period of recovery, but he or she has sufficient reserve to avoid additional complications and to rebound fully to the same level as the patient who received a standard quality liver. A "sick" patient— that is, one who has a high MELD score, prolonged pretransplant course in the intensive care unit, and/or is physically frail—is more vulnerable to a complicated posttransplant course. If transplanted with a standard quality liver, a patient who is very sick at the time of transplant can immediately derive the benefits of the new liver to minimize the severity of postoperative complications. Even if the patient enters into the "zone of adverse outcomes" (Fig. 1) to develop acute kidney injury, wound infection, or intraabdominal abscess, he or she will have sufficient reserve that comes from a healthy liver to avoid escalation of these complications such as dialysis, wound dehiscence, or septic shock. In contrast, a sick patient who receives a marginal-quality liver is at a high risk of experiencing a cascade of postoperative complications. An episode of acute kidney injury can lead to dialysis, preventing timely initiation of the calcineurin inhibitor, resulting in acute rejection, necessitating high-dosed corticosteroids, predisposing him to hospital-acquired pneumonia, and so on. One complication after another prolongs the hospitalization and impedes recovery of his or her physical and nutritional status, further jeopardizing the ability to fully recover from the surgery and derive maximal benefit from a liver transplantation.

This conceptual relationship is strongly reflected in clinical practice: transplant clinicians systematically accept higher-quality livers for higher-MELD patients.[24] There are also objective data to support this relationship. The combination of donor quality and recipient transplant MELD score strongly impacts costs of transplantation, with posttransplant costs rising synergistically with increases in both the MELD score and DRI (ie, as recipient sickness and donor quality worsen).[25] DCD status and older donor age (>40 years) are the 2 strongest drivers of cost.[25] Further underscoring the relationship between donor quality and recipient illness is the metric, D-MELD, calculated from the multiplicative product of

donor age and recipient preoperative MELD score, which predicts both length of stay and survival after liver transplantation[26] Using D-MELD, a patient with a laboratory MELD score of 25 receiving a liver from a 30-year-old donor would have a 4-year expected survival of 77%, but this would be expected to decrease to 62% if transplanted with a liver from a 66-year-old donor.

Selecting the Optimal Liver for the Very Sick Patient

For the very sick patient, donor quality can make the difference between life or death after transplant (Fig. 1). However, the decision to proceed with liver transplantation must also take into consideration the patient's ability to wait for the "ideal" liver, which, for the very sick patient, may be measured on the order of days or even hours. How does one balance these 2 seemingly competing interests?

We have developed a framework to guide this decision to proceed with liver transplantation (Fig. 2; adapted from Flint et al.[27]).[28] In this framework, the clinician should consider the patient's vulnerability to adverse outcomes in 2 broad categories:

1. Transplant responsive, such as liver function and portal hypertension.
2. Transplant nonresponsive, such as nonliver comorbidities and physical frailty.

The patient's specific characteristics within the transplant nonresponsive category are the ones that will impact posttransplant outcomes because those are the characteristics that will not reverse after liver transplantation (or, in the case of something like sarcopenia, will take so long to reverse after transplant that these patients are still highly vulnerable to a rocky posttransplant course). What makes donor quality such a critical factor in the decision to proceed with liver transplantation is that it has the power to shift the direction of the patient's posttransplant course:

- For a "healthy" patient (patient A), a marginal-quality liver can lead to complications that lengthen the hospitalization, require transfer to a rehabilitation facility, and result in readmission, but ultimately, this patient likely returns to their precirrhotic baseline, albeit after a prolonged recovery period.
- For a "very sick" patient (patient C), an ideal liver can maximize the probability that even a "very sick" patient (patient C) will withstand the treacherous perioperative period and derive significant long-term benefit—with respect to both survival and quality of life—from liver transplantation.
- For a "very sick" patient (patient C), a marginal-quality liver risks increasing the patient's short-term and longterm vulnerability to adverse outcomes, leading to very poor quality of life and even death.

It is this last case—the very sick patient receiving a marginal liver—that presents the greatest challenge in transplant decision making. Even though death pretransplant is imminent, liver transplantation with a marginal liver is not likely to result in a clinically meaningful recovery. It is this last case in which liver transplantation is futile.

In conclusion, for the very sick patient, liver donor quality matters. Although most patients can achieve reasonable outcomes with most livers, transplantation of very sick patients with the most marginal of livers minimizes the chances of success for both the recipient and the allograft.

Abbreviations

CIT	cold ischemia time
DCD	donation after cardiac death
DRI	donor risk index
MELD	Model for End-Stage Liver Disease
PNF	primary nonfunction

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Key Points

1. When it comes to maximizing allograft function, the recipient is just as important as the liver graft itself.
2. Donor age, donation after cardiac death status, cold ischemia time, and macrovesicular steatosis are key drivers of posttransplant outcomes.
3. There is a negative synergistic effect between lower donor quality and recipient Model for End-Stage Liver Disease score on posttransplant outcomes.
4. Liver donor quality should impact the decision to proceed with liver transplantation for the very sick patient.

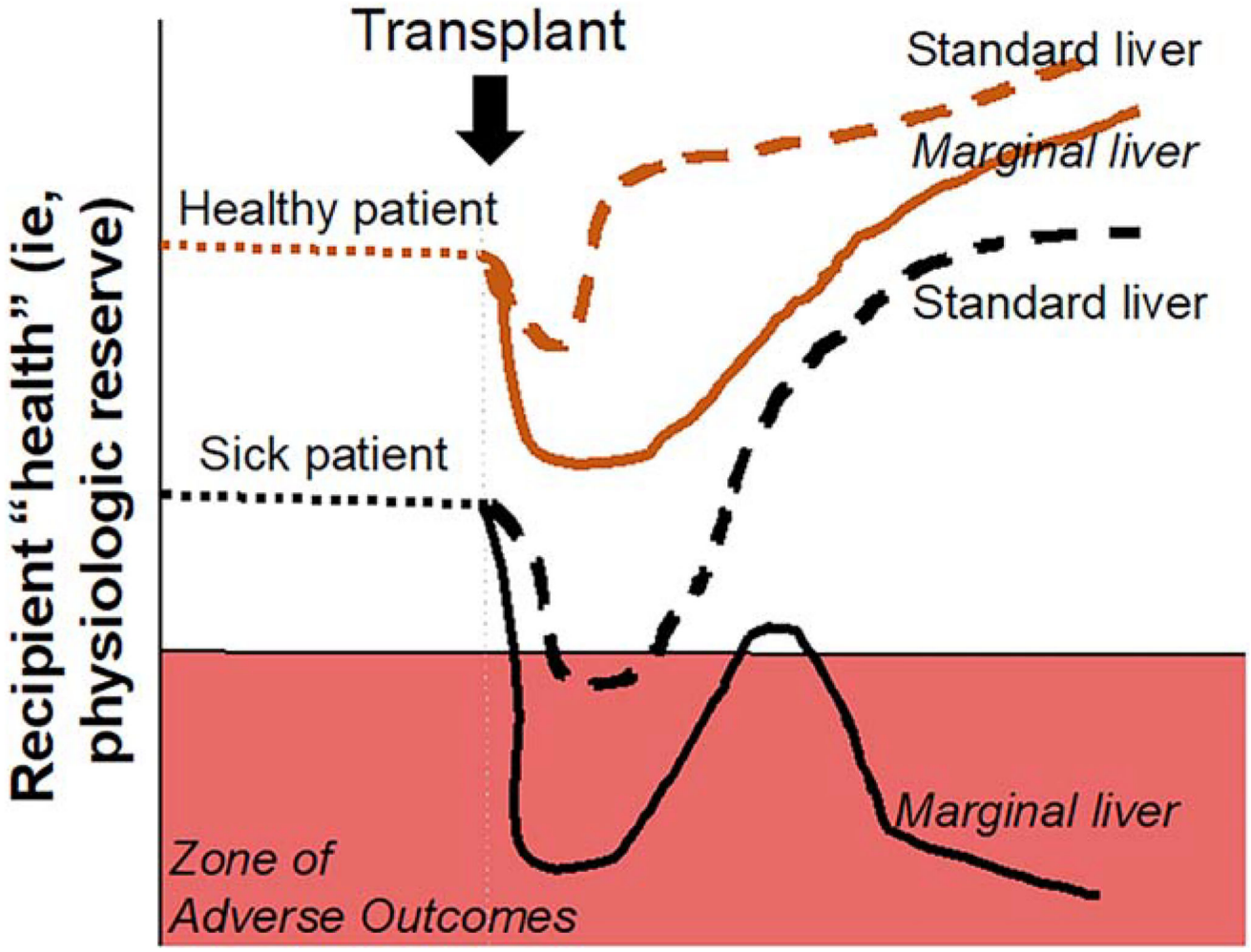

FIG. 1.
Schematic for the hypothesized negative synergistic effect of liver donor quality and recipient illness on posttransplant outcomes.

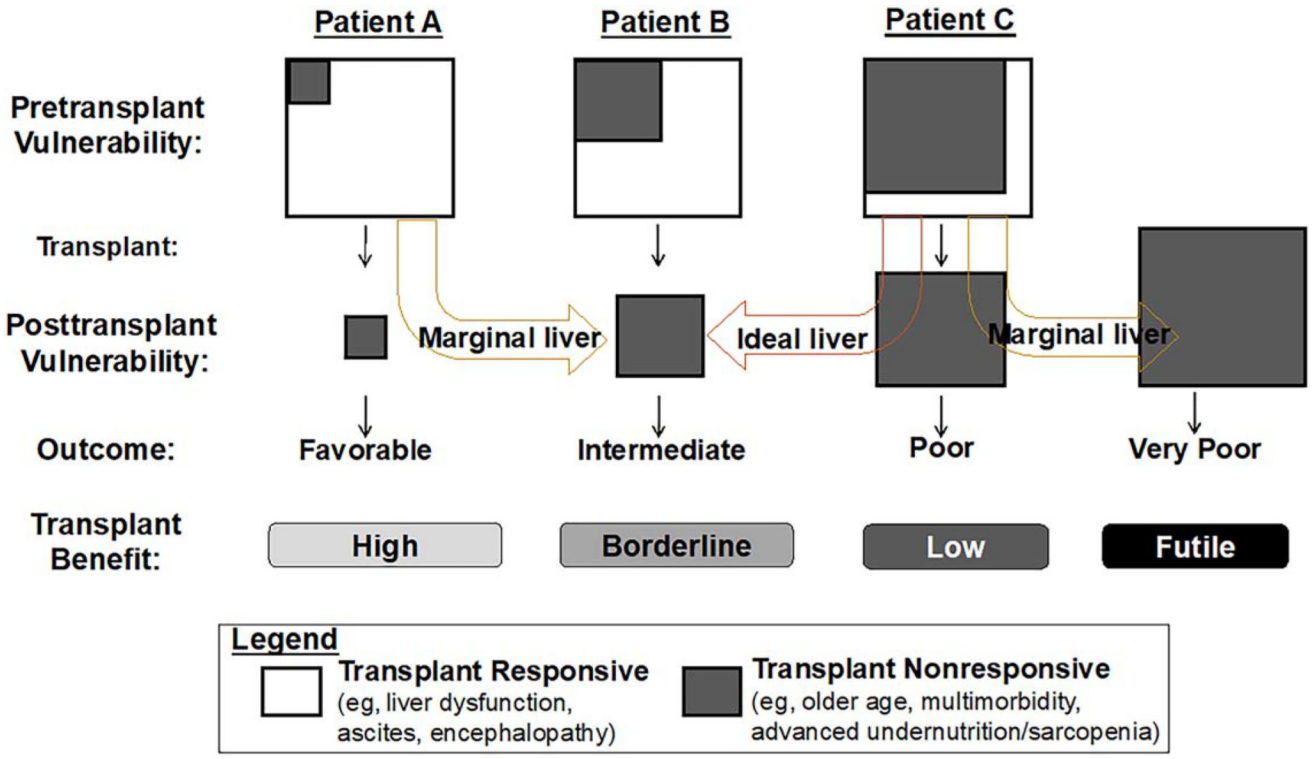

FIG. 2.

Conceptual framework to guide decision making to proceed with liver transplantation with a marginal-quality liver.