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REVIEW

Deceased donor risk factors influencing liver transplant outcome

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Summary

As the pressure for providing liver transplantation to more and more candidates increases, transplant programs have begun to consider deceased donor characteristics that were previously considered unacceptable. With this trend, attention has focused on better defining those donor factors that can impact the outcome of liver transplantation. This review examines deceased donor factors that have been associated with patient or graft survival as well as delayed graft function and other liver transplant results.

In the early development of liver transplantation, clinicians were very conservative in selecting what was thought to be donor livers that were most likely to function well. This was driven partially by the fact that patient selection and transplant surgery themselves were not well understood. Both factors contribute significant uncertainty to the outcome of the transplant so liver teams did not want to introduce more uncertainty by using donor organs that were thought to carry additional risks. However, as much more evidence for selecting appropriate candidates has accumulated and the surgical procedure has become more standardized and routine, along with an increasing demand for transplantation, attention has been directed toward understanding a broader range of donor factors that can influence the outcome of liver transplantation.

Over the last several years, numerous investigators have identified many liver donor factors that are important contributors to patient outcome. These studies have been facilitated by the existence of much more robust databases in which donor and recipient variables are collected for outcome analyses. In the following sections, five main categories of donor factors will be reviewed; donor demographics, donor diseases, donor cause of death and mechanism of death, donor allocation factors, and composite scores. For simplicity, this paper will address only deceased donors and focuses mostly on the donor risks themselves, recognizing that it is the combination of donor risks, recipient factors, and many other details that ultimately determine the success or failure of a given liver transplant procedure.

Demographics

Donor age

There is a large body of evidence dating back more than 20 years documenting that the age of the donor is an independent risk factor for both liver transplant graft and

patient survival. This is probably partially because of the well-documented phenomena observed in animal models of liver regeneration where older animals consistently have rates of hepatocyte and other hepatic cell types regenerating that are slower and less complete compared with younger animals. More recent reports analyzing large transplant registries have confirmed the animal models [1,2], livers from older donors do not seem to recover from damage as rapidly or completely as those from younger donors. Nonetheless, there are also many smaller studies reporting excellent results using liver grafts from donors in their 70s [3,4] or even in selected donors greater than 80 years old [5,6]. These results with older donors highlight the fact that both donor and recipient factors contribute to long-term results and that utilizing organs from older donors must be weighed in the context of all the risks candidates face waiting. Reports advocating for matching donor factors with recipient risks to achieve more optimal outcomes are common and this issue will be addressed later in this review.

Livers procured from older donors after cardiac death (DCD see below) also have poorer results [7,8]. In addition, as cited above, age is associated with the rate and extent of liver regeneration. Since the DCD protocol frequently induces more ischemic damage to the liver, livers from older DCD donors which are subjected to more sever ischemic stress are less able to recover from this damage.

First reported by the group from Valencia, donor age is not only associated with overall patient and graft survival, it is also an independent predictor of hepatitis C (HCV) recurrence and fibrosis progression [9], after liver transplantation [10]. This phenomenon has been observed with DCD livers as well, with preliminary results indicating that, within similar donor age strata, the rate of fibrosis progression is not substantially different for DCD livers compared with organs procured from standard brain dead donors (DBD) [11]. These data provide further evidence that both donor and recipient factors are important for determining the results of liver transplantation. This has led some observers to advocate for preferentially allocating livers from younger donors to candidates with HCV [11,12].

Sex and size

As data have accumulated in large registries, evidence has accumulated that the gender of the donor is associated with liver transplant outcome [13]. Several reports suggest that female donors, regardless of whether the recipient is male or female, are associated with inferior patient and graft survival [14–16]. However, in the largest registry reports, donor sex has not been consistently identified as a factor associated with transplant results [17]. This may indicate that gender of the donor is more a surrogate for graft size than a risk factor by itself. Size matching of whole organ grafts to candidate body size has long been recognized as an important factor for transplant results. More recently, data exist suggesting that larger whole organ grafts from DCD donors have better outcome than right lobe grafts from split livers suggesting that adequate graft size may be more important when ischemic damage is likely to be more severe [18]. On the other end of the graft-size spectrum, small for size syndrome is the well-recognized extreme of small grafts given to larger recipients. However, it is unknown whether this syndrome occurs to a lesser degree in cases with less size mismatch that could also influence graft function and results. Vascular complications may also be more common in size-mismatched grafts, particularly in pediatric recipients, because of technical difficulties encountered when anastomosing vessels of significantly different calibers [19].

Race

Mismatched donor and recipient race has been recognized as a factor influencing liver transplant outcome for more than 10 years. More recently, large multivariable analyses have consistently identified donor race as independently associated with graft survival. In particular African origin has been independently associated with a 19% higher risk of graft failure [17] in the US. However, black recipients, especially if they have Hepatitis C, fare better if they receive a race-matched donor liver compared with receiving liver grafts from Caucasian donors [20]. Whether this is true in European countries is unknown. Interestingly, Hispanic donor ethnicity has not been associated with liver graft survival and, in some reports, may be associated with improved results.

Graft anatomy

With the advancement of surgical techniques, most common vascular anomalies found in the deceased donor liver circulation can be successfully reconstructed during implantation. The pressing demand for more organs has pushed surgeons to develop new techniques for splitting whole liver grafts into two components to enable transplantation of two recipients with one liver. The best results have been reported when the donor liver is divided into segments 2 and 3 (left lateral segment) and segments 1, 4–8 (right trisegment) grafts. This technique has provided great benefit for small children waiting for transplant, as they are ideal candidates to receive the left lateral segment grafts [21]. Although some investigators, using multivariable analyses, have found graft type (split versus whole) is associated with a higher risk for graft failure [17], many other studies have suggested no difference in outcome, especially for these right trisegment/left lateral segment splits [22,23].

These outstanding results have not been so easy to reproduce when the donor liver is split into right (segments 1 and 5–8) and left (segments 2–4) lobes in an effort to transplant two adults. In one small series, full left lobe grafts achieved similar patient and graft survival for highly selected adult recipients compared with full right lobe grafts although overall graft survival was generally lower (65.1% at 1 year) and vascular complications higher, than for whole organ transplantation (20.9% at 1 year) [24] in this series. At this time, grafts for two adults obtained from this right lobe/left lobe split technique should be considered at increased risk for graft failure [25].

Donor disease

Many investigators have identified pre-existing diseases in donors that can impact liver graft function and overall outcome. It is difficult to completely determine causative relationships since age, diabetes, vascular disease, obesity, and steatohepatitis are all related. All of these separately, and together, can impact the livers tolerance to injury and its ability to regenerate after injury.

Donor obesity

Although donor obesity *per se* has only been implicated as having an association with pediatric liver transplant outcomes [26,27], obesity is correlated with steatohepatitis. Many reports have found that significant steatohepatitis is more directly associated with liver graft function, primary graft failure, and longer term graft and patient survival than donor diabetes or obesity [28,29] and recently, studies suggest that macrovesicular steatohepatitis is more strongly associated with graft function than the donor risk index [30] (see below). As experience accumulates and the donor shortage worsens, more centers have reported improved selection criteria for steatotic livers but indicate that even when these grafts ultimately function adequately, the post-transplant course is much more complicated and resource intense [31]. As might also be expected, since older donors are more likely to have more severe steatohepatitis, age and steatohepatitis together pose significantly greater risks for graft failure compared with younger donors [32]. Nonetheless, mild to moderate steatohepatitis has not been consistently associated with increased delayed graft function or primary failure rates although results can be difficult to interpret because methods for determining the amount of steatosis are not standard, inclusion of micro-, or macro-, or both types of fatty infiltration is variable [33], and cutoff values defining mild, moderate, and severe fatty infiltration differ among studies. Importantly, steatosis should be considered a continuous variable with the cutoff values in the literature only used as guides for those making organ acceptance decisions with care taken to remember that these cutoffs are designed more for statistical convenience than for absolutely accurate clinical decision making.

HCV and other donor infections

It is well recognized that infections transmitted from donors to recipients can have important influences on outcome. Cytomegalovirus (CMV) infection, especially when transmitted to a previously unexposed recipient, increases the risks for fungal infections, rejection, accelerated recurrence of HCV infection, and is associated with poorer graft and patient survival [34]. The development of effective prophylactic and pre-emptive regimens has significantly limited the deleterious effects of CMV in liver transplantation. Epstein–Barr virus (EBV) transmitted from an infected donor to a naïve host can similarly pose a risk for post-transplant lymphoproliferative disease and patient death [35]. This is particularly a problem for pediatric recipients who are much more likely to have never been exposed to EBV virus [36].

Transmission of other donor-derived bacterial, viral, and parasitic infections frequently results in adverse sequelae for liver recipients although this phenomena occurs less frequently than CMV or EBV transmission since these other infections are generally less prevalent in the donor population. The rare transmission of HIV from donors to naïve liver recipients has resulted in recipient deaths as have cases of transmission of lymphochoriomeningitis virus [37,38]. Interestingly, documented cases where donor bacterial infection has been transmitted resulting graft or patient failure are rare, likely because of the use of cidal antibiotics in the recipient immediately after transplantation which do not require much participation from the host immune system to eradicate the infection [39]. Donor cancers have also been reported to develop in liver recipients, which mostly have been fatal [40]. Thus, older donors who, by virtue of being older, carry increased risks for harboring cancer and should be carefully screened for occult malignancies at the time of donation.

In 1994, the Centers for Disease Control in the US issued guidelines to try to define which behavioral characteristics might be indicative of a higher risk of transmitting HIV [41]. Although these have received much attention in the professional literature and lay media, these criteria have not been validated in the deceased donor population. Presently, it remains unclear if these are highly predictive of an increased risk of transmitting HIV. However, current US policy requires that potential recipients of organs from donors who bear these behavioral characteristics should be informed of the possibility that there is an increased risk of transmitting HIV in these cases.

Many investigators have reported results for intentionally using liver grafts from donors known to be infected

with either HCV or hepatitis B (HBV). Several reports document that livers procured from HCV+ donors that have minimal histological evidence of fibrosis achieve similar results when transplanted into HCV-positive recipients compared with HCV- livers used to transplant HCV-positive recipients [42,43]. Similar results have been achieved using HBV-positive donors for HBV-positive recipients [44] and there is mounting evidence that anti-HBc-positive, HBsAg-negative livers used for HBV naïve recipients can achieve good results when suitable HBV prophylactic treatment is provided [45].

Donor cause/mechanism of death

In general, the literature suggests that donors dying of traumatic brain injuries yield organs that function better. Although younger donors are more likely to die from trauma, multivariable analyses frequently find that both donor age and traumatic cause of death are independently associated with better organ function after transplant [46]. Trauma usually results in a more severe stress response and potentially more catecholamine release that can negatively affect organ preservation and function [47]. This suggests that, since young trauma victims tend to have fewer chronic diseases, chronic disease comorbidities in the older nontraumatic donor may be more important in influencing liver graft function than the traumatic stress response. Because the average age of the deceased donor population is increasing every year [48], donor comorbidities will become increasingly important in determining overall liver transplant results.

This aging of the donor population comes to the fore when considering donation after cardiac death (DCD). In most developed countries, the incidence of brain death is decreasing [49] because of less overall head trauma and better neurosurgical care of patients with severe traumatic, hemorrhagic or ischemic brain disease. This has driven organ procurement organizations and transplant professionals to increasingly consider utilization of organs from DCD donors [50]. Livers obtained from these donors, particularly from older donors [51] or those with prolonged hypotension or warm ischemia times [52], have significantly higher risks of primary nonfunction and delayed graft function and are now well recognized to be associated with a higher risk of developing ischemic biliary strictures. Data from both the US and Europe indicate significantly higher rates of biliary complications when older DCD livers are used for transplantation [53]. Since the biliary complications associated with DCD liver donation may be related to the biliary vasculature being less well perfused [54] thereby increasing the ischemic insult to the biliary tree in the DCD scenario, it is likely that the increased burden of vascular disease in the older population further contributes to this ischemic damage. Studies by Mathur and others suggest that livers procured from DCD donors more than 50 years of age, African race [55], or from those for whom the time from withdrawal of ventilator support to declaration of death is more than 60 min are much more likely to have poorer results [56,57]. Some researchers have suggested that withdrawal to death declaration time should not exceed 30 min to reduce the risk for delayed graft function, primary nonfunction, or development of ischemic biliary stricture [8,58] and others have related the risk of these negative outcomes to prolonged periods of donor systolic blood pressure less than 50 mm/hg [52]. Some other small studies have suggested that stasis in the biliary arterial tree is responsible for the biliary tract ischemic in the DCD protocol and there are small series suggesting that infusion of anticoagulants such as tissue plasminogen activator in the donor hepatic artery before reperfusion can help ameliorate this problem [59]. Others have advocated for re-vascularizing the donor liver via the hepatic artery first, before the portal vein, as another way to improve the arterial biliary blood flow in these DCD donor livers. In one analysis of the US OPTN database researchers found that DCD donor livers did not confer a worse outcome for HCV-positive recipients compared with DCD livers given to non-HCV recipients [11]. Nonetheless, large series continue to report that livers from DCD donors even when selected for donor age and short ischemia times, still carry increased risks for delayed graft function, primary nonfunction, and biliary complications.

A recent report describing 10 cases from Spain has indicated that livers from highly selected uncontrolled DCD donors can be used successfully if the donor is maintained on normothermic extracorporeal machine preservation. These authors state that these donor organs should be considered extended criteria and therefore are at higher risk of graft failure [60].

Allocation factors

In general when deceased donor livers are offered, transplant programs take into account all of the demographic and donor-specific variables outlined above to determine whether to accept an offer. Many reports from Europe and the US indicate that liver grafts that have been turned down by many centers have poorer rates of function compared with those accepted after the first few offers. In the US, liver grafts are distributed on a geographic hierarchy with transplant centers close in proximity to the donor hospital getting the first offers. Livers are then offered regionally or finally nationally if no local or regional center is willing to accept the graft. These nationally shared livers have been associated with poorer outcomes in general [17] although some single center studies report reasonably good success

[61]. Frequently livers shared over larger geographic areas can accrue longer ischemia times and there is ample indication that deceased donor grafts, whether from DBD [62] or DCD [63] donors, with significantly longer ischemia times have higher risks of graft failure [64]. More recently, however, it is interesting that both in the US [62] and in Europe [65], the characteristics of these "last resort" offers are not widely different than the grafts that are accepted much more readily in the offer sequence and, in some studies, there is no adverse effect on outcome compared with the other liver grafts. These data suggest that much of the "risk" attributed to these so called "rescue offers" of last resort may be in perception rather than objective and valid factors that actually confer additional risk to these grafts.

Composite scores

Several investigators, recognizing that there are many variables that are associated with increased risks of delayed graft function, primary graft failure, or other poor outcomes, have developed composite risk scores that include a variety of donor factors. In most of these efforts, researchers have used multivariable models to derive factors that are independently associated with graft loss. Feng *et al.* [17] published the first analysis in 2006 in which they identified the following independent donor factors: donor age, donor race, donor cause of death, donor height, DCD donor, and partial or split graft, along with regional or nationally shared organ and cold ischemia time. They fitted these in a model and termed this result, the Liver Donor Risk Index (LDRI). It is interesting to note that the data used to derive the LDRI were from the pre-MELD era and moreover, some of these factors in more recent analyses have not been consistently verified as associated with liver transplant outcome [66,67]. Interestingly, donor liver steatosis was not included in the LDRI derivation because the OPTN database did not include this variable. Importantly and not surprisingly, donor age carries the most weight in the LDRI. Consequently, as described above, the donor age-driven LDRI also correlates with HCV recurrence after liver transplantation in which donors with higher LDRI are associated with a greater risk of recurrence and more rapid fibrosis progression [68,69]. A composite score from Europe revealed that in addition to the variables included in LDRI, adding latest lab GGT and rescue allocation proved to be a more accurate model for predicting graft failure in the European cohort [70].

Donor-recipient matching

Considering all of the donor risk factors outlined above and the fact that candidates also carry varying degrees of risk for poorer outcome, several groups have developed algorithms for matching donor organs to recipients based on their collective risk profiles [71,72]. All of these have been aimed at maximizing post-transplant survival and have not taken into account an overall intent-to-treat assessment of the entire patient pool who are candidates for liver transplant regardless of whether the transplant is done. In an intent-to-treat analysis, it is difficult to justify matching the highest risk candidates to lower risks grafts since this would provide only a fraction of the available donor pool to the patients most at risk for dying without the transplant. Limiting the opportunity for transplant for these high-risk candidates by only offering them lower risk donor grafts increases the risk that the very ill waiting candidates will die more frequently. The evidence clearly suggests that even using higher risk grafts in these patients results in a survival benefit relative to not receiving a transplant at all [73]. Importantly, several studies have pointed out that using the higher risk graft for candidates who have relatively low risks of dying while waiting, actually exposes these patients to higher mortality risks compared with not doing the transplant. Therefore, the practice of using the higher risk grafts for lower risk recipients to maximize post-transplant outcome only should be mostly curtailed.

Costs

US results indicate that the use of organs with high LDRIs is associated with increased hospital costs that are independent of recipient risk factors [74]. Across each MELD score category, resource utilization and the hospital length of stay increases 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 post-transplant survival. Evidence from the UK and Europe also supports higher costs for using higher risk organs in higher risk candidates.

Conclusion

Many donor-related factors have been associated with liver transplant outcome and there is much wider recognition that these, in addition to recipient factors, surgical and center experience, all play a role in determining the ultimate outcome of liver transplantation. Because the risks of death are greater for the more ill patients on the waiting list than most of the donor-related risks, higher risk grafts should be considered in these cases. However, directing more grafts to higher risk candidates in pursuit of improving the overall survival benefit of liver transplantation will cost more. This is a fact that the transplant community and the governments and payers who fund liver transplant will need to come to grips with.

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