Review Article

Liver transplantation: expanding the donor and recipient pool

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Abstract: Liver transplantation is an exemplar model of complex surgery and the only curative option for patients with end-stage liver disease. Although historically associated with poor outcomes, liver cancer management has also been revolutionised with liver transplantation and in some instances, survival outcomes are comparable to surgical resection. As such, the key elements underpinning the major advances in surgical technique, immunological therapies and allocation policies combined with improved patient and graft survival outcomes have created a huge demand for organ donation. Despite improvements in donor and recipient selection, there is a persistent disparity between organ supply and demand. Candidate wait-list mortality and dropout rates remain problematic and this concern has resulted in increased efforts to expand the donor pool to meet the unmet needs of the population. This is even more challenging when coupled with an ever-growing recipient pool, candidate waiting lists and an ageing population. Over the past two decades, there has been a considerable focus on extended criteria organs, donations after cardiac death and alternative avenues for marginal liver use. With careful donor selection and recipient matching, these livers may help bridge the gap between supply and demand and placate the ever-expanding recipient pool. Here, we present a summary of recent developments by the transplant community addressing the issues of a growing donor and recipient pool.

Keywords: Liver transplantation (LT); expanded criteria; donor pool; recipient pool

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Introduction

The number of candidates added to the transplant wait list continues to grow. In 2019, 8,896 liver transplants were performed in the United States (US) and the rate has been gradually increasing over the last decade (1). The current annual transplant rate of adult candidates actively listed on the wait list is 58.7% in the US and has increased incrementally compared to previous years. Current 1-, 3- and 5-year survival rates are 91.8%, 83.8% and 76.1%, respectively, and liver transplantation (LT) is being considered for a growing list of conditions evident by the expanding recipient pool and waiting lists. Despite the benefits of LT, the scarcity of organs is a universal concern and there have been several attempts by the transplant community to propose strategies to overcome the deficit. This has led to the consideration of livers which were previously considered unsuitable for transplantation and efforts to optimize "marginal" organs using innovative machine technology. We, herein, provide a brief overview of the existing approaches by the transplant community to expand the donor and recipient pool for LT.

Extended criteria donation to increase the donor pool

The disparity between supply and demand has led to the consideration of extended criteria donor (ECD) liver allografts or "marginal donors" which do not meet the traditional criteria for organ donation. The aging population, longer life expectancy rates and the rising incidence of several metabolic conditions such as obesity, diabetes and fatty liver disease are all important factors contributing to poor donor quality. Such issues are projected to decrease donor liver utilisation rates from 78% to 44% if ECDs are not included in the pool (2). While these organs were previously avoided due to the fear of primary non-function (PNF) or delayed graft function (DGF), they are now increasing used with the goal of improving access to transplantable organs (3). The underlying concern is the graft's susceptibility to ischemia/reperfusion during the transplantation process, adding to graft dysfunction and poor regeneration (4). Despite this risk, ECDs have played an important role in expanding the donor liver pool with compelling evidence demonstrating their ability to reduce wait list mortality and exhibit recipient outcomes comparable to standard liver donations (5,6). There is no universally accepted definition for what constitutes an ECD, however, frequently cited characteristics are advanced donor age, donation after cardiac death (DCD), hepatic steatosis, split liver transplantation (SLT), and donors with an infectious risk or previous malignancy (3,7,8).

Accepting donors with an advanced age

The use of livers from older donors is becoming more frequent in modern practice, despite the concern of DGF during the immediate post-operative period (7,9,10). No clear age cut-off exists and several transplant units are expanding that which is considered an acceptable donor age in an effort to match the increased demand to the ageing population demographic and available donor pool (11). In 2014, 8% of liver donors from the US were 65 years and older and this group increased further to 10% in recent Organ Procurement and Transplantation Network (OPTN) data (12,13). In a report from the European Liver Transplant Registry, Adam *et al.* observed that 29% of donors were older than 60 years and 11% were 65 years or older (14). Some studies have reported acceptable outcomes in livers from older donors. In an early study by Zapletal *et al.* comparing liver allografts from donors both older and younger than 80 years, comparable results were achieved in the postoperative course and older livers grafts were functionally stable at discharge (15). Several other units mirrored similar results in liver allografts from donors over 60 years and in some studies favourable outcomes were achieved from donors older than 70 years as the transplant community continues to explore an acceptable upper age limit (16-18). In a recent study using the United Network for Organ Sharing (UNOS) database, Haugen *et al.* reported a significantly lower 5-year cumulative mortality rate for patients who accepted livers from donors >70 years when compared to a matched control group who declined the same offer (23% *vs.* 41%) and the authors demonstrated a substantial long-term survival benefit in the former group (19). Despite these favourable outcomes, judicious matching of older donors is paramount as these grafts are more susceptible to ischemia reperfusion injuries, biliary complications, a slight preponderance for hepatic artery thrombosis and the risks are particularly heightened in donors with hepatitis C (17,20,21).

Increasing DCD

Livers from donors with irreversible brain injury, not meeting the criteria for brain death, have resulted in the expansion of the donor pool. A study by Saidi *et al.* reported an increase in the utility of DCD organs from 4.9% to 11.7% during a 10-year study period (22). In the case of LT, recent OPTN data suggests an increase from 4.8% to 6.9% in DCD livers between 2008 and 2018 (12). Several studies comparing DCD livers with standard brain-dead donors (DBD) have demonstrated poorer allograft and patient survival rates in the latter. This is likely related to the longer ischemia time associated with DCD donors, commencing from the time of extubation until cold perfusion, which can be highly variable. A large multicentre study of 2,572 liver transplants comparing DCD and DBD livers identified that 3-year graft loss and recipient mortality were twice as high with DCDs (23). In contrast, a study by Taner *et al.* noted no differences in 1-, 3- and 5-year patient survival rates between DBD and DCD groups and similar comparable outcomes for graft survival (24). In an effort to determine factors leading to graft loss, the authors identified a link between the asystole to cross clap duration and the development of ischemic cholangiopathy, an important and feared consequence of DCDs. Nonetheless, DCDs can significantly and safely expand the donor pool when used with caution, adhering to a warm ischemia time less than

30 minutes, using donors younger than 50 years and limiting cold ischemia time (7,8). Future efforts to minimize ischemia times and expand the upper age cut-off will further increase the utility of DCD livers and expand the donor pool.

The use of steatotic livers

The rising incidence of obesity and metabolic syndromes has led to the commensurate rise in non-alcoholic fatty liver disease (NAFLD), with a population prevalence of up to 30% in Western societies (25,26). These rising incidences and prevalence rates have seen parallel increases in potential donors with hepatic steatosis. Traditionally, steatotic allografts were avoided in LT for posing significant clinical challenges in terms of early graft dysfunction and PNF. An early study by Spitzer and colleagues analyzing a large US registry of transplant recipients conclusively established that livers with 30% or greater macrovesicular steatosis were associated with lower 1-year survival rates (27). Similar studies have demonstrated unfavourable outcomes in the use of grafts with moderate (30–60%) and severe (>60%) steatosis, largely due to the increased susceptibility of steatotic grafts to ischemia reperfusion injuries (28,29). However, in an effort to further expand the donor pool, fatty livers are increasingly considered for transplantation and form a major component for ECDs. In well matched cases, mild steatosis may have a minimal impact on reperfusion injury and post-transplant hepatic functionality. A study by Dutkowski and colleagues analysed both US and European liver transplant registries and determined grafts with microvesicular and 30% or less macrovesicular steatosis can be used safely with outcomes comparable to non-steatotic livers (30). Acceptable outcomes were also achieved in steatosis greater than 30% with careful risk adjustment, although this remains controversial. Similar studies assessing the suitability of steatotic grafts have also considered the use of moderate to severely steatotic allografts with somewhat acceptable post-transplant outcomes, provided they are supplied by low-risk donors (31,32). Continuing to extend the upper limits of steatosis and define the acceptability of steatotic grafts will still be a matter for debate, however, the integration of these grafts into the donor pool has been a key element in providing more livers for transplant.

Considering donors with an increased infectious risk

The use of donors with exposure to hepatitis B (HBV) or C (HCV) virus has been more acceptable in current times, albeit previously met with strong objection due to initial concerns regarding the introduction of aggressive viral strains to immunosuppressed recipients. In the context of HCV, there has been a shift in previous attitudes and recent OPTN data reports an increase in the number of livers recovered from hepatitis C positive donors and the number of wait-list candidates willing to accept these livers (12). Rigorous matching remains pertinent and younger donors are preferred due to the fear of increased fibrosis in recipients when older HCV positive donors are used (33). Hepatitis C positive recipients transplanted with positive donors have demonstrated comparable outcomes to those receiving HCV negative livers (34,35). In an effort to further expand the donor pool for all patients, transplanting HCV positive livers into HCV negative patients, with the addition of effective antiviral regimens, has seen some promise in terms of long-term outcomes. Chhatwal and colleagues report compelling evidence demonstrating that accepting HCV positive livers for all donors may increase life expectancy and decrease wait-list mortality (36). Additionally, a recent study by Cotter and colleagues analysing data from 2008 to 2018 reports increased 3-year graft survival rates from 79% to 88% in HCV negative donors receiving HCV positive livers and direct-acting antiviral therapies (37). Similarly, the increased use of organs from HBV positive donors has the potential to expand the donor pool. In a study by Cholongitas and colleagues, recipients without prior exposure to HBV receiving antiviral prophylaxis showed excellent outcomes following transplantation with HBV positive livers (38). Effective HBV prophylaxis in the form of hepatitis B immunoglobulin or oral antiviral therapy have led to a reduction in HBV transmission and viral recurrence in select donors and some units have included these in their donor pool (39-41). While this practice is still limited to a few centres because of the concern of viral reactivation in recipients, more effective prophylaxis could encourage the inclusion of such grafts for the wider recipient pool.

Split liver grafts

Splitting livers (SLT) into two potential grafts has been explored as another method to increase donor supply, however, their use has been relatively stable over the last decade (12). This procedure usually involves donating the left lateral segment to a pediatric recipient and transplanting the right trisegment into an adult, although splitting the liver into a right and left lobe for two adults has also been described (7,42). It has been estimated that up to 20% of livers are suitable for splitting, however, the technique is limited to specialist centres due to the complexity of the procedure and the heightened risk of biliary and vascular complications (42,43). A study by Vagefi and colleagues assessing outcomes in SLT recipients reported 93%, 77%, and 73% and 89%, 76%, and 65% overall patient and graft survival rates at 1-, 5- and 10-years (44). A similar study by Doyle and colleagues demonstrated 95.5%, 89.5% and 89.5% 1-, 5- and 10-year survival rates in adults recipients of SLT, comparable to whole organ (WLT) recipients (45). In contrast, a multicentre study by Aseni demonstrated lower 5-year survivals in patients receiving SLT compared to WLT (63.3% *vs.* 83.1%) (46). While SLT continues to be limited to centres with technical expertise, they require high quality grafts to gain acceptable post-operative outcomes and currently only represent 1% of US liver transplants and 6% of transplants in Europe (12,47).

Living donor LT (LDLT)

First reported in the US in 1998, LDLT is an additional mechanism to expand the donor pool and increase organ availability. Both right and left lobes can be used in transplantation with the latter generally reserved for small sized recipients and paediatric patients. A left lobe resection has the added benefit of removing a smaller portion of liver from the living donor. By contrast, the right lobe, mainly reserved for adult patients, accounts for up to two-thirds of the total liver mass and can potentially cause significant harm to the donor if the remnant liver volume is too small or unhealthy to support the metabolic and physiological needs of the recipient. The number of LDLTs has increased slowly over the past 2 decades and recent US liver registry data reports LDLTs accounted for up to 4.4% of liver donations in 2018 (12,48). Although modest, the increase in LDLTs has been largely driven by a rise in the number of unrelated directed donors (12). The number of left lobe resections has also decreased corresponding with a parallel rise in right lobe donations. A study by Shah and colleagues demonstrated significantly shorter mean waiting times between right lobe donations and patients awaiting grafts from deceased donors (49). Although LDLT has the advantage of optimizing the timing of surgery, comprehensive donor work-up and minimizing cold ischemia and organ transport times, the process still poses a risk to the donor and can subject a healthy person to a substantial burden (50). Overall donor mortality rates range from 0.2% to 0.8% with some studies reporting a slight donor survival benefit in right lobe donations (51-53). Graft failure is reported to occur in up to 7.8%, 14.6% and 26.5% of LDLTs at 1, 3 and 5 years with more favourable outcomes demonstrated in non-hepatocellular carcinoma (HCC) diagnoses and Model for End-stage Liver Disease (MELD) scores less than 20 (12). Furthermore, a study by She and colleagues reported, in an analysis of 218 patients, significantly better 5-year graft survival rates in using right lobe LDLT, albeit comparable 5-year patient survival rates (54). These findings were contrasted by Olthoff and colleagues who in a large multicentre study of 963 LDLTs demonstrated similar graft survival rates in right and left lobe LDLTs with decreasing rates of graft failure associated with greater centre experience (55). However, despite these promising results several studies have reported inconsistent graft survival rates between LDLT and standard cadaveric liver donations. Some analyses have demonstrated decreased graft survival rates in LDLT (56,57), while more recent studies appear to demonstrate similar long-term 10-year survival rates between patients receiving grafts from living donors and deceased donor grafts (55). For this reason, LDLT is reserved for high volume centres with specialist expertise due to the complexities of the procedure which requires a deep understanding of the physiological requirements of the graft to ensure sufficient hepatic regeneration and minimize donor risk.

Machine perfusion to optimise liver quality

The recent arrival of *ex-vivo* machine perfusion techniques is beginning to change the landscape of how "marginal" livers are utilized and has the potential to fully expand the donor pool and reduce liver discard. Hypothermic and normothermic machine perfusion technologies have shown promising results in minimising injury to DCD grafts and steatotic livers (58,59). Schlegel and colleagues provided 5-year outcome data on patients receiving DCD liver transplants following treatment with hypothermic oxygen perfusion prior to transplantation. Outcomes of treated DCD livers were similar to DBD and superior to untreated DCDs with significantly less graft loss events (58). A recent study reported similar encouraging results in transplanting previously rejected liver allografts following the application of normothermic machine perfusion (60). While the optimal temperature setting continues to be debated, this innovation may salvage various extended criteria allografts and modify their risk for routine use, ultimately expanding the donor pool.

Expanding the recipient pool

Despite several strategies attempting to increase the liver donor pool, the recipient pool continues to expand and wait list mortality remains a concern. The wider acceptance of LT and improved outcomes has allowed clinicians to consider transplanting patients they were historically reluctant to do so. According to OPTN data, alcoholic liver disease, non-alcoholic steatohepatitis (NAFLD) and HCC are the most common conditions leading to LT in the US and the increased public burden of these diseases has contributed to an increased number of patients requiring transplantation (12). The healthcare prevalence of alcoholic liver disease continues to grow. A study by Jinjuvadia and colleagues observed a substantial increase in the number of alcohol-related hospitalizations over an 8-year period (61). In 2018, the proportion of candidates listed for ALD increased considerably from 22.7% to 29.8% over a 10-year period (12). Similarly, NAFLD is becoming more prevalent and has been linked with the alarming growth rate of population obesity (26). Several models have projected this to become the leading cause for LT as more patients progress to decompensated cirrhosis warranting curative intervention. In addition, global trends have demonstrated a rising incidence in the diagnosis of HCC, although the causes of this are still unclear (62). The evidence regarding transplanting HCC patients, particularly since the introduction of the Milan criteria, has been promising for unresectable disease and more patients are being considered for LT and form a substantial portion of the recipient pool (63,64). The proportion of HCC candidates awaiting LT increased from 3.4% to 9.8% between 2008 and 2018 (12). There has been some interest in expanding the current eligibility guidelines for HCC. Yao and colleagues report similar LT outcomes in HCC patients with tumours as large as 6.5 cm or less than 4 nodules smaller than 4.5 cm and a total tumour diameter less than 8 cm, arguing that the current Milan staging is too restrictive (65). Additionally, the success of chemotherapy has seen several patients with advanced disease downstaged to liver disease within the Milan criteria and meeting eligibility for LT (66). Several other hepatic tumours have been added to the recipient pool with promising results in some units. In a small prospective case-series by Lunsford and colleagues, patients with locally advanced intrahepatic cholangiocarcinoma and stable disease from neoadjuvant therapy had 1-, 3- and 5-year survival rates of 100%, 83.3%, and 83.3% respectively. While the study only involved a small selected group of patients, LT showed promise (67). In addition, despite initial reluctance, some units have started to reconsider LT for colorectal liver metastases (CLM). In a study comparing LT and chemotherapy for nonresectable CLM, LT observed better 5-year survival rates (56% *vs.* 9%) (68). Although, this has yet to gain widespread acceptance, better expertise in LT and cancer biology could see a rapid expansion in the recipient pool and the inclusion of patients who were previously contraindicated for LT.

Future directions

The transplant community continues to evolve and active efforts to expand both the donor and recipient pools are in constant motion. LT remains a curative option for a wide spectrum of the population and expertise in surgical technique, immunotherapy and post-operative care are among the several elements underpinning the continually improved outcomes reported internationally. While breakthroughs in machine perfusion and chemotherapy are still underway, the role of social media in increasing awareness of organ donation may be a feasible route. Kumar and colleagues, in collaboration with Facebook, created a mobile application whereby waitlisted candidates were allowed the opportunity to create a post and communicate their experience with organ failure and the need for live organ donation (69). Impressively, candidates who engaged with the app were 6.6 times more likely to have a donor come forward compared with matched controls and the app was received well overall (69). As the boundaries of social media platforms continue to push limits, some have advocated for the increased use of social media billboard approaches and targeted campaigns to shift societal perspectives of organ donation and gain public attention (70).

Conclusions

In summary, LT is a growing field with boundless potential. The disparity between patients who need a liver transplant and those who receive one is a constant concern, and while significant progress has been made in the field, further efforts from the national and international consortia are warranted. Pre-existing criteria for LT and recipient boundaries are continually challenged and expanded and, when coupled with judicious matching and careful patient selection, excellent patient and graft survival results are an endless opportunity.

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