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

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 clamp 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
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 donors 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...
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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