Update of liver transplantation-newer aspects

Olga METİN MD, Cem ŞİMŞEK MD, Ahmet GÜRAKAR MD,

Correspondence:
Ahmet Gurakar, MD
Division of Gastroenterology and Hepatology
Johns Hopkins University School of Medicine
Liver Transplant Program
Baltimore, Maryland, USA 21205
Phone: 410 614 3369
Fax: 410 614 8741
e-mail: aguraka1@jhmi.edu

Contributions:
OM: Literature review, writing
CS: Critical review, editing
AG: Concept, Literature Review, Editing

Funding:
None
ABSTRACT

Liver transplantation (LT) remains as the only therapeutic option offering gold standard treatment for end-stage liver disease (ESLD) and acute liver failure (ALF), as well as for certain early-stage liver tumors. Currently, the greatest challenge facing LT is the simple fact that there are not adequate livers for all the potential patients that could benefit from LT. Despite efforts to expand the donor pool to include the living and deceased donors, organ shortage is still a major problem in many countries. To solve this problem, the use of marginal liver grafts has become an inevitable choice. Although the definition of marginal grafts or criteria for expanded donor selection has not clarified yet, they usually defined as grafts which may potentially cause primary nonfunction, impaired function or late loss of function. These include steatotic livers, older donors, donors with positive viral serology, split livers, and donation after cardiac death (DCD). Therefore, to get the best outcome from these liver grafts, donor-recipient selection should be vigilant. Alcohol-related liver disease (ALD) is one of the most common indications for LT in Europe and in North America. Traditionally, LT for alcoholic liver disease kept limited for patients who have achieved 6 months of abstinence, in part due to social and ethical concerns regarding the use of a limited resource. However, majority of patients with severe alcoholic hepatitis who fail medical therapy will not live long enough to meet this requirement. Besides, the initial results of early liver transplantation (ELT) without waiting for six months of abstinence period are satisfactory in Severe Alcoholic Hepatitis (SAH). It will be important to take care of these patients from a newer perspective.
Keywords: extended criteria donor, liver transplantation, marginal liver grafts, severe alcoholic hepatitis
1. INTRODUCTION

Since the first procedure performed by Thomas E. Starzl in 1960, liver transplantation (LT) has been as the gold standard for the treatment of end-stage liver disease (ESLD), acute liver failure and some selected liver tumors [1]. Despite the efforts to increase the donor pool by increasing usage of live and deceased donors, there has been an unmet need for donor livers in the United States (US) and universally [2,3]. The demand for liver has been steadily expanding. Only in the US, annually about 11,000 patients with ESLD get enlisted while annual liver transplantations are in the range of 6,000-7,000 [2]. To overcome the organ shortage problem, transplantation centers had to expand their criteria for donor selection. With the expansion of donor suitability criteria, use of marginal grafts has become mandatory. Marginal grafts or expanded donors are grafts which may potentially cause primary nonfunction, impaired function or late loss of function, although there is not a clear-cut definition [3,4].

In this review, we defined marginal grafts as grafts which carry potential risks of early or late loss of function meaning aged donors, donors with steatosis, hepatitis, human immunodeficiency virus (HIV) or split liver or donors after cardiac death.

As post-LT survival rates have been steadily improving, mean age of donors and recipients increase with resulting increase in use of marginal donors. Improvements in surgical techniques, advances in postoperative care and developments in new immunosuppressive medications have also contributed to this. Recent United Network for
Organ Sharing (UNOS) data shows that one-year post-LT survival is around 85-90% and 10-year survival is around 50%.

Before 2002, prioritization of liver transplantation has performed according to Child-Turcotte-Pugh Score. This system was based on the presence of subjective criteria such as ascites and encephalopathy to predict short term mortality risk. To overcome this hurdle, a more objective alternative was Model for End-Stage Liver Disease (MELD) score. After implementation of MELD, wait-list mortality has dramatically declined [5,6,7]. Besides this score, presence of fulminant hepatic failure, metabolic liver disease or complications chronic liver disease such as variceal bleeding, and development of hepatocellular cancer, are also considerable factors to proceed transplantation.

Besides the criteria above, there are some diseases in which MELD score is not directly correlated with survival. These “MELD-exceptions” are hepatocellular cancer, hepatopulmonary syndrome (HPS), portopulmonary hypertension (PPH), familial amyloid polyneuropathy, cystic fibrosis, or cholangiocarcinoma after chemoradiotherapy protocol. Other considerations such as donor age (D-MELD), frequent cholangitis episodes in patients with primary sclerosing cholangitis have been emerging to be important factors that predict prognosis, but they are not MELD-exception points by consensus yet [8,9]. Recently, serum sodium is also included in MELD calculations and used as MELD-Na (especially in patients with low serum sodium) in US [10].

After final decision of LT, screening and evaluation of possible comorbidities is of crucial importance for patients in transplant wait list. Even though post-LT survival rates have increased with recent developments in surgical techniques and medical care, liver
recipients still have less short-term survivals compared to age-sex matched normal population [11]. Most frequent complications are due to cardiovascular diseases in long term follow up of liver transplant recipients. Cardiovascular events comprise almost 19-42% of mortalities in this group of patients [12,13]. Mortality rates increase in ESLD patients who had coronary artery disease by angiography in the pre-LT period [14]. Thus, pre-LT evaluation protocol should be able to detect underlying cardiovascular disease. Single positron tomography, myocardial perfusion sintigraphy and dobutamine stress echocardiography are valuable to evaluate coronary artery disease. Coronary calcium score (CCS) calculated by computerized tomography is known to be correlated with the severity of coronary artery disease and can predict the cardiovascular risk in ESLD patients [15,16].

2. DONOR AGE

Organ shortage in liver transplantation will potentially lead to increased usage of older donors in the future [17]. In US, donors aged more than 50 comprise 33% of donors while in some European countries this ratio increases to greater than 50% [18]. Primary problems with older age donor grafts are impaired regeneration capacity after transplantation, being prone to ischemic and reperfusion injury. These grafts are more vulnerable to hepatitis C (HCV) recurrence and graft fibrosis and cirrhosis develop faster [19,20]. Fortunately, synthetic capacity of liver is similar in older grafts due to the dual blood supply [21].

Definition of old donor shows variability among different transplantation centers. Age threshold can change in between deceased donor liver transplantation (DDLT) and living
donor liver transplantations (LDLT). Most of the studies has defined age threshold between 65-70 years in DDLT while 50-60 years in LDLT [22,23]. One study calculated liver volumes after LDLT in postoperative 7th day and 3-6 months, and compared them with donor age< 30 years versus donor age >50. In patients with donor age >50, regenerative capacity of the liver decreased with age as independent risk factor [19]. In the case of LDLT, condition of the recipient is not the sole problem, as the donors’ survival and complication rates after hepatectomy are at least of equal importance. Impaired regeneration capacity increases morbidity for both the donor and the recipient. Regeneration problem is not important in DDLT as whole liver is used as graft [24]. Previous studies showed that in LDLT donor age >50 or 60 resulted in lower patient and graft survival rates if the recipients were old, HCV positive and MELD score is greater than 20[20,23,24,25,26]. Postoperative complication rates and severity were found to be similar between donors <50 years of age and donors >50 years of age [26,27].

A few studies showed that in HCV positive recipients, graft loss, recurrent HCV infection followed by hepatic fibrosis and development of cirrhosis was faster when donors were older. A recent consensus held in Paris recommended not to use older grafts in HCV positive recipients [22,28,29]. However, at the same time, cure of HCV infection is possible with direct acting antiviral drugs. Treatment of HCV infection in live donors before or after transplantation might enable us to use older donor grafts in HCV positive recipients. In a short time, older grafts used in LDLT will potentially result in better patient and donor survival rates if used in HCV negative recipients with low MELD scores, if they do not have steatosis or increased ischemia time due to technical reasons.
3. LIVER GRAFT STEATOSIS

Hepatic Steatosis has two subgroups: macro- and microsteatosis. Microvesicular steatosis is not associated with poor prognosis after transplantation, in opposite macrovesicular steatosis is associated with primary or early weak donor function [30]. Why does macrovesicular steatosis lead to poor graft function? Its pathogenesis is not exactly clear. However, macrovesicular steatosis leads to impaired hepatic microcirculation which makes liver more susceptible to cold ischemia and ischemia reperfusion injury [30]. Grafts with lower than 30% steatosis in grafts is not associated with worse post-transplant prognosis. On the other hand, grafts with 30-60% steatosis are preferable when donor has normal liver functions, donor is under 60 years of age, cold ischemia time below 8 hours, with good graft removal conditions in recipients who have following criteria: HCV negative with MELD score lower than 20. In the cases of recipients or donors with greater than 30% steatosis, the transplant team should consider the above risks [31].

Liver steatosis is a more important topic in living LDLT than DDLT since it increases both donor’s and recipient’s morbidity due to the poorer graft functions [31,32]. Previous studies showed no relationship of primary or early poor graft functions with steatosis up to 30% [33,34,35]. In mild steatosis up to 60%, showed similar both graft and recipient’s survival rates with nonsteatotic grafts if graft volume is higher than 40% of standard liver volume. Severe liver steatosis effects both graft and recipient’s survival rates [36]. Biliary complications were more often in these grafts in first three months after transplantation. Besides, survival rates of grafts with severe steatosis (>60%) were significantly shorter and approximately 25% in one year [37]. Similarly, a recent meta-analysis reported that grafts
with moderate to severe steatosis showed lower survival rates compared to grafts with no steatosis or mild steatosis. Macrovesicular steatosis also increases the probability of poor graft functions (PNF) [30].

Unlike cadaveric liver transplantation, steatosis in living donors may be reversible. A short-term intense protein rich diet, exercise, drugs like fibrates and omega-3 fatty acids may reduce liver steatosis. In some studies, these methods reduced steatosis successfully in donors and improved the postoperative outcomes of donors and recipients [38,39].

4. OBESITY

Obesity is increasing all around the world and this is threatening liver donor pool. According to 2012 data, 69% of entire population in the US was overweight (body mass index (BMI) >25) and 35% was obese (BMI>30 [40]. Obesity is a known strong risk factor for liver steatosis. In a study, 76% of BMI≥28 living donors had steatosis in liver biopsies [41].

Graft steatosis is associated with worse outcomes in recipients after liver transplantation. These include ischemia reperfusion injury, biliary strictures, primary graft failure and lower survival rates in one year [42,43].

Although negative effects of graft steatosis are well-known effects of obesity alone without steatosis on liver transplantation are controversial. Recent studies reported that in selected obese donor groups (BMI ≥30 but ≤35) of non-steatotic livers and without accompanying cardiovascular comorbidities including hypertension, diabetes mellitus and
dyslipidemia; donor hepatectomy may be feasible. Both, recipients of donors with BMI >30 and donors had similar outcomes with donors BMI <30 in short and longterm. Obesity is also a risk factor for postoperative complications. These complications include pulmonary infections, delayed wound healing and wound infection, and thrombotic events [44,45].

Length of hospital stay is longer in obese patients and all cost of treatment is higher [46].

Knak et al. has observed that people with obesity without liver steatosis and cardiovascular comorbidities may safely become donors [47]. Dindo et al. evaluated elective surgical results of 6336 patients and reported that %26 of them were obese. They concluded that obesity was not a risk factor for postoperative complication rate [48].

5. CHRONIC HEPATITIS OF GRAFTS

Both donors’ and recipients’ infection with hepatitis viruses affect post-transplant outcomes. Previously, HBV or HCV positivity in grafts were an exclusion criterion for transplantation. Along with prophylaxis against hepatitis B virus (HBV) via development of HBV vaccine, use of Hepatitis B immunoglobulin and use of nucleoside analogs; leaded to use of Hepatitis B surface antigen (HBsAg) and Hepatitis B core antigen (HBcAg) positive grafts in liver transplants [49]. Similarly, development of direct acting antiviral agents (DAA) against HCV leaded to transplantation of HCV infected liver grafts to both HCV positive and negative recipients [50].

Grafts in anti HBcAg antibody (HBcAb) positive donors carries risk of HBV transmission and most of these donors have occult HBV infection [51]. After
transplantation of HBcAb positive grafts, risk of De novo HBV (DNHB) infection in HBV naïve recipients is 58% higher; the risk is observed lower in previous HBV vaccination or HBV infection (HBsAb+, HBcAb+) [52]. Previously grafts with HBcAb positive donors were used in HBV naïve recipients, DNHB risk found to be lower in these recipients with the use of lamivudine [52].

In the light of all these data American Society of Transplantation (AST) consensus guideline recommends long term treatment of HBV naïve recipients with HBcAb positive donors with nucleoside analogs with prophylactic purpose [53].

Since the rapid transmission and progression of HBV infection in grafts, and cause the loss of 50% of grafts in two years, chronic HBV was a definite contraindication for liver transplantation in the 1980's [54,55]. Hepatitis B immunoglobulin and following antiviral treatment lead to dramatic results in clinical outcomes. Nowadays, outcomes of posttransplant chronic HBV patients have better outcomes than other transplantation indications [56,57]. Nevertheless, HBsAg positive grafts without delta hepatitis and without histologic signs of liver disease are considerable for liver transplantation [58]. Any HBV infected patient should take antiviral treatment. Posttransplant HBIG administration is a common practice in transplant centers depending on the recipients’ risk status to keep HBsAb titers between 100-500 IU/ml [53].

In the aspect of HCV; HCV positive grafts were only transplantable to HCV positive recipients previously [59,60]. Due to the potential post-transplant transmission of HCV to the recipient and course of HCV in untreated patients, transplantation of HCV positive grafts is still uncommon [61]. Direct acting antiviral agents (DAA) are both very effective
in the treatment and well tolerated in patients with HCV infection. DAA has success rates above 95% [62]. HCV positive grafts have similar graft and recipient survival rates in HCV negative recipients if periportal fibrosis (F2 Ishak) is absent in pretransplant period [63]. HCV viremia or De novo HCV infection is detectable by positivity of HCV RNA in serum. Mean time for positivity is one week after transplantation [53]. Recurrent HCV infection warrants a prompt treatment. Laboratory, clinical or histologic findings should not cause a delay. The choice of DAA depends on the patients’ immunosuppressive regimen and potential drug interactions. AST guideline recommends start of pan genotypic agent in early posttransplant period without delay for genotype analysis [53].

6. HUMAN IMMUNODEFICIENCY VIRUS

Worldwide prevalence of Human Immunodeficiency Virus (HIV) reached 37 million [64]. With the development of antiretroviral treatment, HIV infected patients have reached normal lifetime, and HIV unrelated causes has become major determinants for their survival [64]. Liver disease is one of the leading causes of death unrelated to AIDS reaching 10% [64]. An important reason for this increased prevalence is concomitant infection of HBV and HCV with HIV, reported as more than 10% and 30% respectively [64]. Thus, promotion of organ transplantation in this population is of great importance, since the survival rates of HIV infected recipients are comparable to noninfected recipients albeit three times higher acute rejection rates.
First efforts to transplant HIV positive organs were hampered by the poor outcomes in 1980’s resulting strict prohibitions in many countries. A decade later following the advent of antiretroviral therapies, transplant from HIV patients deemed feasible. Particularly in countries with high HIV prevalence, liver transplantation from HIV positive donors has become an appealing option. Moreover, nearly two thirds of HIV positive patients are willing to donate their organs with HIV positive recipients. They have unique motivations such as overcoming the HIV related stigmas and empathy for other infected patients [65].

Muller from South Africa Republic spearheaded HIV positive organ transplantation. In his pioneering series, 27 HIV infected patients had kidney transplantation from HIV infected donors. In these patients 3- and 5-years graft and recipients survival rates found to be similar with non-HIV infected counterparts. After similar reports from United Kingdom and Switzerland [66], HIV Organ Policy Equity (HOPE) Act passed in the US in 2013. With this law, start of HIV positive organs as grafts has begun in US. In March 2016, first liver transplantation of HIV positive recipient from HIV positive donor was in Johns Hopkins University [67]. For now, HIV positive organs are transplantable only to HIV positive patients. First-time transplantation of HIV positive organ to HIV negative recipient in the world was in South Africa Republic in 2017. In this case, HIV positive mother donated her liver to her baby with biliary atresia. Special ethic committee decision and legal permissions followed by a standard transplant surgery. Before the surgery, mother had antiretroviral treatment and baby had preoperative prophylaxis. One year after the transplantation both baby and mother were both in good condition. With this
transplantation, probability of usage of HIV positive organs in HIV negative patients is considerable [68], albeit the long-term results remain unclear.

A recent study explored another benefit of HOPE act. Every organ is pre-screened for HIV antibody and nucleic acids before pursuing transplantation, however these tests are known to have nonnegligible false positive rates. Before the act, these organs were unusable if either one is positive, but with the act the organs are transplantable to seropositive recipients. Estimated number for this organ pool is 50-100 per year in US [69].

7. DONOR AFTER CARDIAC DEATH

Since the 1990’s, organs of donors after brain death (DBD) have been used in many transplantation centers. Organs of donors after cardiac death (DCD) consists 5% of all cadaveric donors [70,71]. Notably, these organ donation procedures have started right after determination of death by cardiorespiratory criteria. Quality of donor is the most important factor determining peri- and post transplantation organ functions. In a meta-analysis consisting 25 studies, evaluated outcomes of 62000 liver transplantation recipients.

Ischemic type biliary strictures commonly observed in livers from DCD with a reduced total graft and recipient’s survival [72]. Although, the mechanism of ischemic cholangiopathy is unclear, possible mechanisms are longer duration of hot ischemia causing blood stasis and clots in peribiliary microcirculation [73,74].
8. SPLIT LIVER GRAFTS

Split liver transplantation (SLT) is sharing of liver of an adult cadaver donor between an adult and a child recipient. SLT has become an option to increase donor pool in child patients. After SLT, complications such as biliary leaks, biliary strictures, hepatic artery thrombosis are more common in adult recipients than children in 10 years [75,76]. These complications are less frequent in further years [77,78]. A successful SLT depends on three factors including careful recipient and graft selection, reducing risk factors associated with bad results and trying to keep cold ischemia time as short as possible during liver splitting [79].

SEVERE ALCOHOLIC HEPATITIS

Alcohol-related liver disease (ALD) is the most common indication of liver transplantation in Europe and US [80]. Severe alcoholic hepatitis (SAH) is the presence of jaundice and hepatic decompensation in individuals who consume excessive alcohol [81]. Short term mortality of these patients is high, and six months’ mortality is less than 30% [82,83]. Corticosteroid treatment is useful if not contraindicated and some patient groups do not respond to steroid treatment. For these patients, liver transplantation is the only option [84]. Traditionally, liver transplantation in ALD patients awaits 6 months of alcohol cessation, due to limited donor pool with social and ethical concerns [81]. Unfortunately, most of these patients cannot survive even six months to complete this abstinence period [81]. Hence, early liver transplantation is considerable for severe alcoholic hepatitis. First study was from Europe by Mathurin et al. including six centers from France and one center
from Belgium between 2005 and 2010. In this study, 26 patients had liver transplantation and survival rates have increased significantly in six months and two years [83]. Following this article in 2011, nine patients with SAH after liver transplantation in US from Mount Sinai hospital had similar results [82]. Six months survival rates were as high as 89% in transplanted patients [82]. Larger study from Johns Hopkins including 46 carefully selected SAH patients who had undergone LT, had similar 1-year outcomes (97% patient survival and 93% graft survival in the SAH group) and recidivism (28% in the SAH group), when compared to 34 patients with more than 6 months of sobriety [84].

All these studies showed that early liver transplantation in selected patients with SAH who fail to respond medical treatment may benefit from liver transplantation with a six months’ survival rates of 77% and 100% [82,84].

The American Consortium of Early Liver Transplantation for Alcoholic Hepatitis (ACCELERATE-AH) group evaluated results of early liver transplantation of 147 patients with SAH without waiting 6 months of alcohol abstinence period in 12 transplantation centers and reported that one-year survival as 94%, and three-year survival rate as 84% (85). Data from Europe and US confirms the need for reconsideration of the rule of 6 months alcohol abstinence period [80].

Alcohol consumption after liver transplantation is a major problem for both ALD and SAH. Studies showed similar rates of reuse of alcohol for early liver transplantation compared to late transplantation after 6 months of abstinence period. In a prospective study conducted by Di Martini et al, 167 patients with transplantation after 6 months of alcohol
abstinence, the alcohol recidivism rates were 21% and 32% in one year and three years, respectively [86].

In the American Consortium study by Lee et al.[85], the alcohol recidivism in 147 SAH patients with early LT were 25% and 34% in one and three years, respectively. Studies showed similar rates of alcohol relapse in early liver transplantation (transplantation in 6 months) and transplantation after 6 months of alcohol abstinence period [87]. These studies support for reconsideration of 6 months of alcohol abstinence period in ALD. Patients with SAH who failed to respond medical treatment have a survival rate of almost above 80% after liver transplantation. But reuse of alcohol increases the morbidity and graft loss, especially in heavy drinkers. The major problem is still reuse of alcohol in these patients.

10. CONCLUSION:

In this review, we aimed to discuss the requirement for marginal liver grafts caused by limited donor pool and increasing need for liver transplantation. Marginal grafts are associated with poor graft outcomes. In the light of the data, careful patient and graft selection may contribute to better outcomes. Graft pool is insufficient, and demand is rapidly increasing. Marginal grafts still seem to be the only option to increase donor pool. Besides, results of early liver transplantation without waiting for six months of abstinence period are encouraging in SAH. Care of such patients needs a newer perspective, especially for selected groups.
REFERENCES


15. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA 2004;291(2):210-5. DOI: 10.1001/jama.291.2.210

16. Detrano RC, Doherty TM, Xiang M, Kawakubo M, Labree L et al. Comparison of calcium scores from thick- and thin-image slice-computed tomography scanning in
DOI:10.1013/j.amjcard.2003.11.034

DOI:10.1097/MEG.0000000000000322


DOI:10.1007/s00268-012-1496-1


39. Marsman HA, Heger M, Kloek JJ, Nienhuis SL, ten Kate FJ et al. Omega-3 fatty acids reduce hepatic steatosis and consequently attenuate ischemia reperfusion injury following
DOI:10.1016/j.dld.2011.07.009


55. Lucey Mr, Graham Dm, Martin P, Di Bisceglie A, Rosenthal S et al. Recurrence of hepatitis B and delta hepatitis after orthotopic liver transplantation. Gut. 1992;33(10):1390-1396. DOI:10.1136/gut.33.10.1390


70. Johnson RJ, Bradbury LL, Martin K, Neuberger J. Organ donation and transplantation in the UK—the last decade: a report from the UK national transplant registry. Transplantation 2014;97:S1–S27. DOI:10.1097/01.TP.0000438215.16737.68


