Liver Transplantation 2023: Status Report, Current and Future Challenges

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Liver transplantation offers live-saving therapy for patients with complications of cirrhosis and stage T2 hepatocellular carcinoma. The demand for organs far outstrips the supply, and innovations aimed at increasing the number of usable deceased donors as well as alternative donor sources are a major focus. The etiologies of cirrhosis are shifting over time, with more need for transplantation among patients with alcohol-associated liver disease and nonalcoholic/metabolic fatty liver disease and less for viral hepatitis, although hepatitis B remains an important indication for transplant in countries with high endemicity. The rise in transplantation for alcohol-associated liver disease and nonalcoholic/metabolic fatty liver disease has brought attention to how patients are selected for transplantation and the strategies needed to prevent recurrent disease. In this review, we present a status report on the most pressing topics in liver transplantation and future challenges.

Keywords: Alcohol-associated Liver Disease; Alcoholic Hepatitis; Allocation; Equity; Extended Criteria Donor; Fatty Liver; Hepatitis B; Hepatitis C; Liver Cancer; Machine Perfusion; MELD; Xenotransplantation.

Global Liver Disease Burden and Liver Transplantation Activity

Deaths due to cirrhosis constituted 2.4% (range, 2.3%–2.6%) of total deaths globally in 2017 compared with 1.9% (range, 1.8–2.0%) in 1990, with 10.6 million (range, 10.3–10.9 million) prevalent cases of decompensated cirrhosis in 2017.[1] The age-standardized prevalence of decompensated cirrhosis increased from 110.6 (range, 108.0–113.0) per 100,000 population in 1990 to 132.5 (range, 128.6–136.2) per 100,000 population in 2017.[1] Globally, in 2017, 31.5% of cirrhosis deaths in males were caused by hepatitis B, 25.5% by hepatitis C, 27.3% by alcohol-associated liver disease (ALD), 7.7% by nonalcoholic fatty liver disease (NAFLD), and 8.0% resulted from other causes. Females had a higher proportion of cirrhosis deaths due to NASH (11.3%) and other causes (17.3%) than males, but a lower proportion due to HBV (24.0%) and ALD (20.6%).[1]

The high and increasing cirrhosis burden heightens the need for liver transplantation (LT). LT rates globally have increased but with highly variable access globally. In 2021, there were 34,694 liver transplants performed globally (Figure 1), an increase of 6.5% from 2020 and a 20% increase from 2015 (living or deceased).[2] Use of living donors, donation after circulatory death (DCD) donors, and extended criteria donors represent important means of expanding the donor pool. In the United States (U.S.), the number of LTs has increased ∼18% in the last 5 years,[3] to a total of over 9400 per year, with the greatest proportional increase occurring among living donors and greater utilization of higher risk donors (eg, older donors and DCD). Although deceased donor LT constitutes more than 90% of LT in the Western world, in many Asian countries, most transplants are living donor LT (LDLT).[2] In the U.S., only 4.3% of LT used living donors in 2020, though both deceased donor and, to a much lesser extent, LDLT in the U.S. have been rising.[4]

Abbreviations used in this paper: **ACLF, acute-on-chronic liver failure; AFP, alpha-fetoprotein; AH, alcohol-associated hepatitis; ALD, alcohol-associated liver disease; AUD, alcohol use disorder; CCA, cholangiocarcinoma; CI, confidence interval; CRLM, colorectal liver metastasis; D, donor; DAA, direct acting antivirals; DCD, donation after circulatory death; DM, diabetes mellitus; GLP-1, glucagon-like peptide-1; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus; HMP, hypothermic machine perfusion; HOPE, hypothermic oxygenated machine perfusion; iCCA, intrahepatic cholangiocarcinoma; ICI, immune checkpoint inhibitor; INR, international normalized ratio; LT, liver transplantation; LDLT, living donor liver transplantation; MELD, Model of End-stage Liver Disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NMP, normothermic machine perfusion; R, recipient; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; U.S., United States.**

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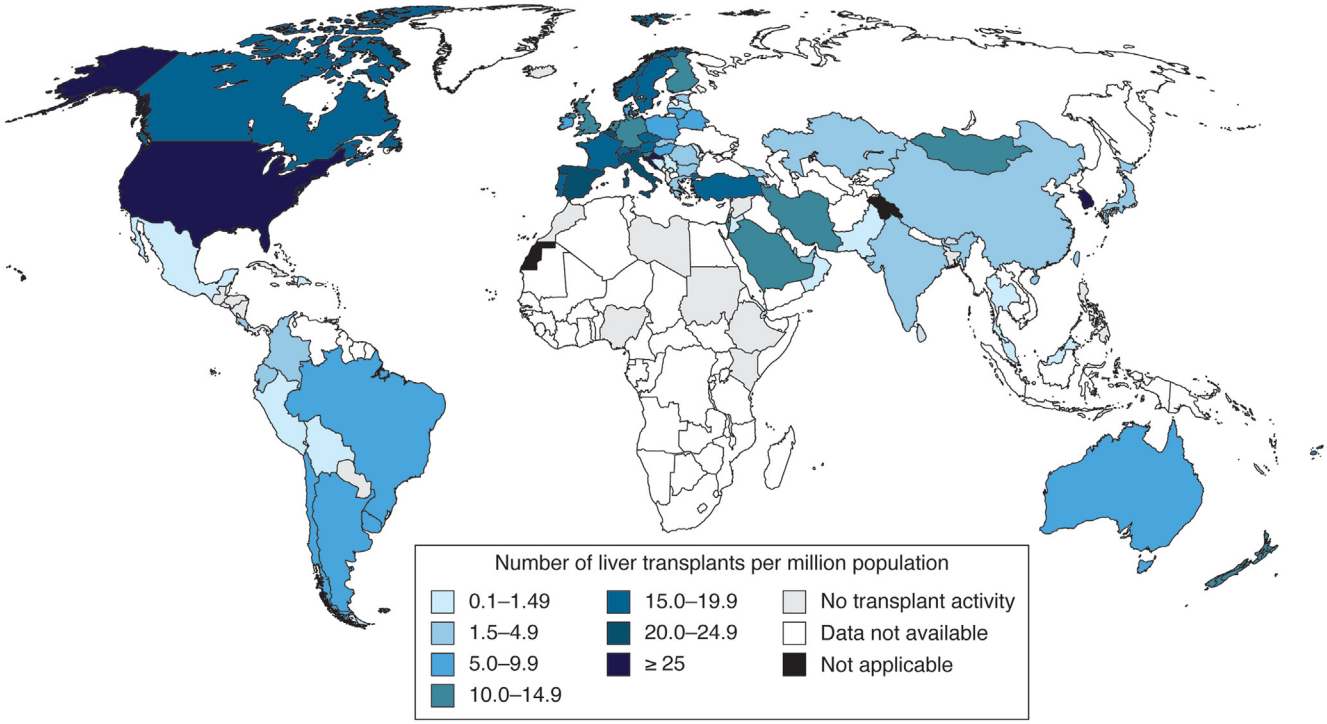

Figure 1. Global liver transplant activity in 2021 per million population. Overall, 34, 944 liver transplants were performed, with 23% using living donors. The highest number of transplants per million population are seen in Korea, the United States, and several countries in Western Europe. Data source: Global Observatory on Donation and Transplantation. Accessed January 2, 2023.

Etiologies of cirrhosis leading to LT differ by region in the world and are changing over time. Despite advances made in the treatment of hepatitis B and C, viral hepatitis remains the principal cause of cirrhosis and liver cancer in Southeast Asia, Africa, and the East Mediterranean regions. In the U.S. and Europe, dramatic decreases in hepatitis C virus (HCV) as indication for LT have been seen since 2014 when direct-acting antivirals (DAAs) became available.[5] ALD is the most frequent indication for LT in Europe, and in recent years, has become the most common indication in the U.S. Globally, the proportion of LT performed for NAFLD-related complications is lower than viral hepatitis and ALD, but this indication is increasing rapidly and anticipated to become the most common indication for LT in many countries within the next decade. In the U.S., the proportion of LT for nonalcoholic steatohepatitis (NASH) increased from 2.5% in 2004 to 20.4% in 2019[6]; in Europe, from 1.2% in 2002 to 8.4% in 2016[7]; and in Japan, from 2% in 2007 to 11.5% in 2017.[8]

Current Challenges in Liver Transplantation

Liver Graft Allocation Policies, Prioritization on the Waiting List and MELD Deficiencies

In the context of a chronic organ shortage, efforts have been made during the last decades to refine allocation policies, with the aim of minimizing waiting list mortality, while giving guarantee of excellent post-transplant survival. In 2002, the Model of End-stage Liver Disease (MELD) score was proposed as the core system for organ allocation and implemented in the U.S. first, then in most Western countries.[9] The MELD score, an objective measure incorporating 3 quantitative values (serum creatinine, international normalized ratio [INR], and serum bilirubin), has proven to be a robust predictor of short-term mortality in patients with cirrhosis, including candidates for LT.[10,11] Ranging from 6 to 40, MELD allows precise ranking of patients in large populations in a verifiable and auditable manner, a major issue for regulatory agencies. Importantly, the MELD-based sickest first policy does not result in worse post-transplant outcomes.[12] In parallel to the MELD score, various allocation systems have been developed to prioritize patients with hepatocellular carcinoma (HCC), and adjustments have been done periodically to ensure equity between end-stage cirrhosis and HCC by modifying extra points given to patients with HCC.[13] Incorporation of serum sodium into MELD (MELD-Na) provided a modest improvement in the accuracy of wait list prediction of mortality[14] and was adopted as a standard part of the MELD score in the U.S. in 2016.

The MELD score has recognized limitations.[15] Although the prognostic impact of impaired kidney function in cirrhosis is well-known, the use of serum creatinine as a surrogate marker of renal function is inaccurate, as well as equations using creatinine to

estimate glomerular filtration rate.[16] Using measured glomerular filtration rates helps to overcome inaccuracies, but measurement of clearance of exogenous agents is costly, time-consuming, and impractical for routine use.[17] Efforts have been made to develop more "cirrhosis-oriented" equations, and although more accurate than equations derived from the general population,[18,19] there is no consensus on which should serve as a reference. Women, due to lower muscle mass, have lower serum creatinine than men for the same degree of renal dysfunction, negatively impacting MELD scores.[20] The addition of serum sodium to MELD in the U.S. in 2016, modestly improved[21] the accuracy of predicting 3-month mortality, particularly in patients with ascites. A concern is that serum sodium can be easily manipulated with diuretics. The use of INR in the calculation of the MELD score is also controversial. INR varies according to the thromboplastin reagent used, the type of INR measuring device, and the international sensitivity index chosen.[22] INR is obviously biased in patients receiving vitamin K antagonists, such as those with portal vein thrombosis who may be artificially overprioritized. Finally, the MELD score has been developed when chronic hepatitis C was the leading indication for LT. These patients tended to have high bilirubin levels, possibly due to a persistent intrahepatic inflammatory process. With a shift in the etiologies of cirrhosis including more with NASH-related cirrhosis (Figure 2), the weight given to bilirubin in the existing MELD score has been questioned.[23] Refinements of prediction of wait list mortality have continued, with a recent proposal for MELD 3.0.[24] MELD 3.0 includes 2 new variables, gender and albumin, and gives less weight to creatinine and more weight to bilirubin. Compared with MELD-Na, MELD 3.0 resulted in fewer wait list deaths (7788 vs 7850; $P = .02$) in the liver simulated allocation model analysis and importantly, reduced the well-recognized gender disparity evident with MELD and MELD-Na, and has recently been approved for use in the U.S., with adoption in mid-2023.

Although objective measures are important to reduce biases, some complications of cirrhosis such as refractory hydrothorax, severe encephalopathy, or hepatopulmonary syndrome represent excellent indications for LT, but many of these patients may have low MELD scores, limiting access to LT.[25,26] In the U.S. and other countries, MELD exceptions are used for those conditions associated with mortality but underserved by MELD score. Natural history data should be used to assign prioritization, but for many complications, strong prognostic markers are missing,[25,26] making this process subject to bias. Finally, sarcopenia and frailty have been proven to have independent prognostic value in cirrhosis[27,28] and influence post-LT survival,[29] and thus are relevant in determination of LT futility.

Acute-on-chronic liver failure (ACLF) represents cirrhosis complicated by extra-hepatic organ failure. Although, in the absence of LT, mortality is very high, good results can be achieved with "rescue" LT, with 1-year survival rates exceeding 80% in selected patients.[30-32] The high mortality rate is related to multiple organ failures that may not be captured by the MELD score, with the exception of kidney failure.[33] Post-LT morbidity and mortality is higher in patients with ACLF vs those without but varies with grade of ACLF.[32-38] Improvement in ACLF pre-LT, defined in one study by recovery of at least one previously failed organ system, was associated with better post-LT outcomes.[38] Although some have suggested that a high grade of ACLF may be a consideration for withdrawal of supportive care (ie, transplant futility),[30,39] additional prospective studies with more granular data are needed.

During the last 20 years, substantial changes in the landscape of LT have occurred (Figure 2), with the decline of hepatitis C, the growing burden of NAFLD, older age at transplantation, and more comorbidities. The need for LT still exceeds by far the number of available grafts. Until now, allocation rules have been based on the principle of urgency. However, a balance between urgency, individual transplant benefit, and transplant benefit at the community level should be considered. There is growing evidence that quality of life after transplantation should be considered, which makes the issue even more complex. Whether emerging technologies based on artificial intelligence will be helpful to improve the allocation rules remains uncertain.

Hepatocellular Carcinoma: Expanding Role of Liver Transplantation

HCC is the sixth most frequent new tumor (over 800,000 new cases per year worldwide), with a persistently poor 5-year survival rate, resulting in over 900,000 deaths per year and making it the fourth most common cause of cancer deaths.[40] The potential for LT to cure HCC was recognized from the inception of LT, with the first liver transplant in an adult being performed in a person with HCC.[41] The obvious appeal of LT as a treatment for HCC is the capacity to simultaneously remove the tumor while restoring liver health and greatly reducing the risk of developing new HCC. Utilizing donor organs, whether living or deceased, in a fashion that produces acceptable (defining optimal is highly subjective) utility and equity is one of the great and most dynamic challenges in LT. The challenge is increased in the context of allocation systems that are based on parameters (eg, MELD-Na) that efficiently predict mortality risk attributable to severity of liver disease but are frequently unrelated to waitlist and post-transplant mortality attributable to HCC. The growing incidence of liver disease, the associated increase in incidence of HCC, and the rapid evolution of locoregional and immunotherapies for HCC necessitates a dynamic and persistent analysis of how to define what constitutes an acceptable tumor burden and how to prioritize organ allocation to patients with HCC.

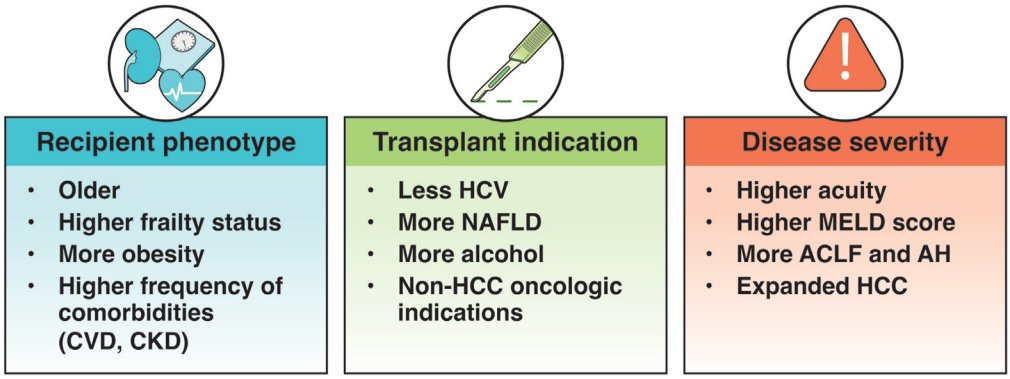

Figure 2. Changing landscape of LT. Over the past decade, the recipient phenotype has changed (older, greater frailty with more comorbidities), LT indications have shifted away from HCV towards more alcohol and non-alcohol associated liver disease as well as broader oncologic indications such as cholangiocarcinoma, and disease severity is greater among those undergoing evaluation and transplantation. CKD, Chronic kidney disease; CVD, cardiovascular disease.

In the U.S., prioritization for LT (a standardized MELD exception) is currently given to patients with T2 HCC lesions if they have an alpha-fetoprotein (AFP) level less than 1000 ng/mL and *either* of the following: (1) one lesion greater than or equal to 2 cm and less than or equal to 5 cm in size; or (2) 2 or 3 lesions each greater than or equal to 1 cm and less than or equal to 3 cm in size. With this background, within current United Network for Organ Sharing organ allocation policy,[42] the following scenarios are considered to be contraindications to LT and/or will not be given MELD exception for HCC:

- Macro-vascular invasion of main portal or hepatic veins;
- Extra-hepatic metastasis;
- Ruptured HCC;
- Resectable or T1 stage (solitary tumor <2 cm);
- Patients who have a history of HCC treated >2 years ago with no evidence of recurrence;
- Patients who were beyond standard criteria that, despite locoregional therapy, have demonstrated progression of tumor burden;
- Patients with AFP>1000 at any time who do not achieve an AFP below 500.

Because of the wide variation in outcomes that can be observed within similar anatomical HCC criteria, many of these contraindications are relative or temporary, rather than absolute. For example, in light of reports of good long-term post-LT and post resection survival in recipients with a history of HCC rupture,[43,44] patients with ruptured HCC or macrovascular invasion of HCC that have remained stable for a minimum of 12 months after treatment may be suitable for consideration of LT. Patients with a history of HCC that was treated >2 years ago who develop new lesions after 2 years can also be considered for LT but with the same criteria and prioritization as those with no prior HCC. Similarly, patients who were initially beyond standard downstaging criteria (up to 5 lesions, total tumor volume <8 cm) that are successfully downstaged to T2, may be considered for MELD exception prioritization 6 months after meeting downstaging criteria.

There are 2 immediate, major challenges in LT for HCC. All of the aforementioned criteria for LT in patients with HCC are based, in part or fully, on risk of tumor extension and recurrence that is assessed by tumor number and diameter. Although these risks certainly increase with increasing AFP, tumor size, and number,[45] biomarkers that more fully reflect tumor and patient biology and, thereby, the risk of tumor extension and recurrence, are a key unmet need in LT. Vascular endothelial growth factor,[46] *Lens culinaris* agglutinin-reactive alpha-fetoprotein (AFP-L3),[47] des-gamma-carboxy prothrombin,[48] and inflammation index (neutrophil-to-lymphocyte ratio)[49] have shown promise in this regard. Preliminary studies suggest a role for molecular biomarkers measured in liquid biopsy, such as circulating tumor cells, in prediction of HCC recurrence that might aid in future candidate selection and/or guide posttransplant management.[50]

The second challenge is increasing our understanding of how to incorporate and manage emerging standards of care for an increasing portion of HCC scenarios, specifically immune checkpoint (ICI) and vascular endothelial growth factor inhibitors. Although the risk of post-LT T-cell mediated rejection in patients who have received ICIs is clearly increased (PD-1/PD-L1 and CTLA-4 pathways are important mediators of graft tolerance), the risk varies between ICIs and with time since administration.[51] Optimal choice of dose and time since administration of ICIs before *and after* LT are rapidly evolving topics that merit prospective, multicenter analyses.

NAFLD as Indication: Surgical and Medical Innovations for Weight Loss in the Transplant Candidate

Obesity has become the most common chronic health condition in the world, and the impact of this epidemic

on liver disease has been dramatic, with NAFLD now estimated to be present in approximately 25% of adults world-wide.[52] NAFLD with or without HCC is now the most common indication for LT for women and the second most common for men.[53]

Although early reports noted worse outcomes for obese LT recipients, contemporary analyses report similar post LT patient and graft survival.[54-57] However, concern about recurrence of NAFLD following LT, as well as the potential of other obesity-related comorbidities to negatively impact long-term post-transplant outcomes, has led to consideration of potential treatment options.[58-60] Additionally, though waitlisted LT candidates with obesity have similar survival benefit with LT as non-obese candidates, they have a lower transplant rate and a higher waitlist mortality rate.[55,61,62]

Although the benefits of weight loss on survival outcomes for either waitlisted or post-LT patients have not been specifically defined, several reports in non-transplant persons with NAFLD have demonstrated improvement in fibrosis following weight loss. Specifically, in paired biopsy studies, those with $\geq$10% total body weight loss had an improvement in fibrosis.[63-65] Additionally, in the general population, bariatric surgery decreases adjusted long-term mortality by 40% (37.6 vs 57.1 deaths per 10,000 person-years; $P < .001$) and is associated with resolution of type II diabetes mellitus (DM) in 50% of patients and reduction in new onset DM by 85% at 12 years post-surgery.[66]

The demonstrated efficacy of bariatric surgery in the non-transplant population, combined with the concern for recurrent NASH[67] or complications such as DM, has led to consideration of bariatric surgery in LT patients, though the optimal timing has not been defined. Elective surgery, including bariatric surgery, is contraindicated in patients with decompensated cirrhosis due to high risk of postoperative death.[68,69] Even among those with clinically compensated cirrhosis, the severity of portal hypertension and degree of biochemical liver dysfunction may influence outcomes. However, there are multiple series of patients with compensated cirrhosis who have successfully undergone bariatric surgery (some reporting higher complication rates).[70-73] In a large single-center analysis of selected patients referred for LT (32 patients, average MELD score 12 with history of prior decompensation) who underwent laparoscopic sleeve gastrectomy prior to being waitlisted,[74] all had successful weight loss with no perioperative deaths. There were 21 who were ultimately listed and 14 who underwent LT. However, a recent analysis of the impact of prior bariatric surgery on waitlisted LT patients (n = 78) did note a higher waitlist mortality rate (33% vs 10%; $P = .002$) and a lower transplant rate (49% vs 65%; $P = .02$), compared with a matched cohort without prior bariatric surgery,[75] highlighting a need for additional long-term data in those with cirrhosis and bariatric surgery.

For patients with decompensated cirrhosis (Figure 3), bariatric surgery can only be considered either simultaneous with or after LT, although the optimal timing is not established. Successful short-term and long-term success has been reported in several case series for combined LT and sleeve gastrectomy, demonstrating the procedure to be safe and effective for long-term management of obesity, with a reduction of obesity-related complications such as recurrent steatosis and diabetes.[76-79] Sleeve gastrectomy is favored over Roux-en-Y because it provides more gradual weight loss as well as preserved access to the biliary tree (and distal stomach in case of gastric varices), which is advantageous in patients with cirrhosis or LT. Bariatric surgery post-LT has also been described in several case series, with the largest reporting on a series of 15 patients who underwent sleeve gastrectomy at a median of 2.2 years following LT, which noted a low complication rate and effective weight loss.[80] The potential advantage of one combined surgical procedure instead of 2 may improve patient access and acceptance, reduce cost, and provide a more rapid resolution of obesity and related comorbidities, although this must be balanced with the logistical challenges and the increased complexity for the recovery from a combined LT plus sleeve gastrectomy.

Non-surgical weight loss options will likely also play an increasingly important role in the optimal management of the obese LT patient (Figure 3). Although the role of novel endoscopic options such as intragastric balloon are evolving, their use will likely continue to be limited in the LT setting by portal hypertension.[81,82] However, the recently approved tirzepatide, a novel combined glucagon-like peptide-1 and glucose-dependent insulinotropic peptide receptor agonist, demonstrated up to 25% total body weight loss (plus a reduction in liver fat content and in NASH biomarkers) and has generated much excitement.[83-85] This joins glucagon-like peptide-1 agonists, semaglutide and liraglutide, which are also approved. There are no data on use of these medications in patients with decompensated cirrhosis or in the post-transplant setting, and cost and availability are additional barriers to their use, but the efficacy is superior to previously available pharmacologic agents. Thus, they have the potential to significantly improve outcomes for all obese patients, including those requiring LT.

Alcohol-associated Liver Disease: Transplant With Limited Sobriety

The global burden of ALD is significant, and trends indicate it will continue to have a social and economic impact in the years to come.[1,86] Of 2.3 billion people that drink worldwide, 40% (ie, 300 to 350 million) are heavy current drinkers, with an increasing number of younger people being diagnosed with ALD. The interaction with several comorbidities, particularly obesity, with the rising numbers of NAFLD[52] and the collateral impact of the pandemic, have increased the incidence and severity of

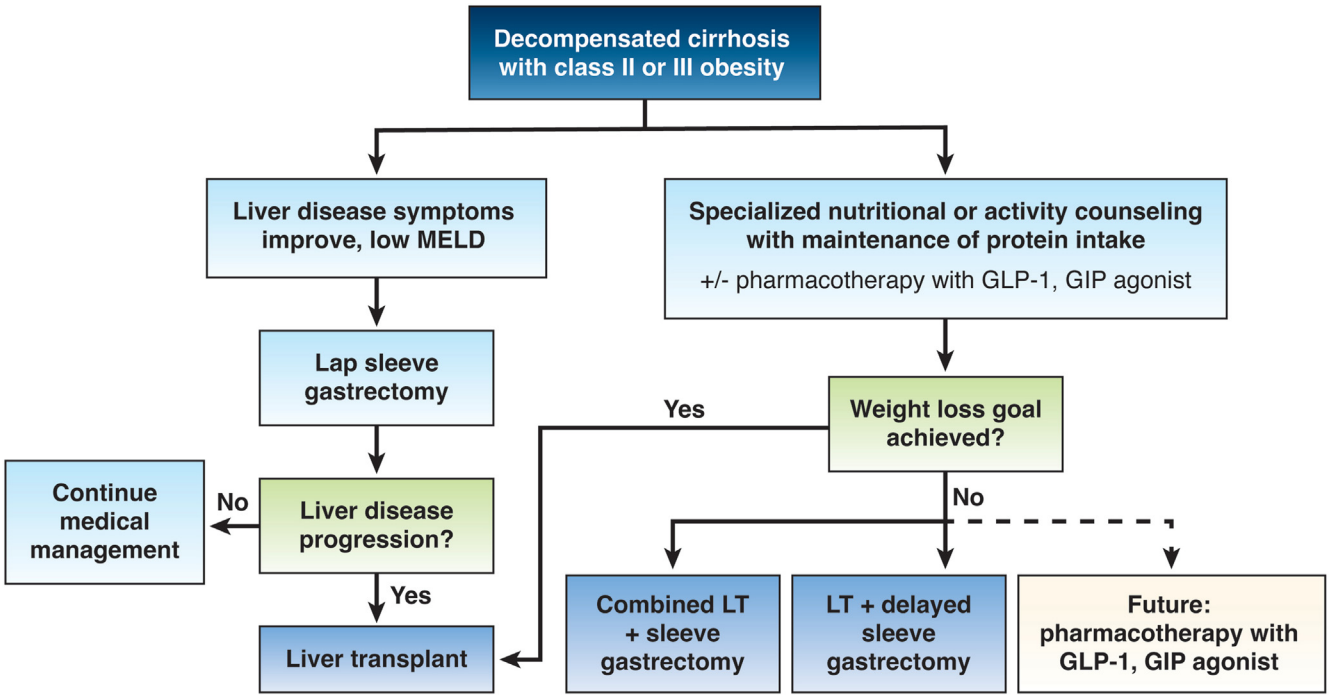

Figure 3. Managing obesity in transplant candidates and recipients. Patients with decompensated cirrhosis are not candidates for bariatric surgery and should be managed with specialized dietary and exercise counseling aimed at achieving weight loss but not loss of muscle mass. If patients with initial decompensation achieve clinical improvement (recompensation), laparoscopic sleeve gastrectomy can be considered pre-LT. For those patients with decompensated cirrhosis who are unable to achieve weight loss goals, either combined LT and sleeve gastrectomy is an option (in experienced centers) or LT with delayed sleeve gastrectomy. Pharmacotherapy with glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide receptor agonist may be a future option.

alcohol use disorder (AUD)[86,87] and led to an unprecedented increase in alcohol-related hospital admissions, including those for alcohol-associated hepatitis (AH),[86-88] and alcohol-related and liver-related deaths, as well as transplant listings.[87-89] Since 2014, ALD has gradually risen as an indication for LT in most countries, concomitant with the significant fall in HCV-related indications, representing about one-third of all indications both in the U.S. and Europe.[90-93] Following the COVID-19 pandemic, many centers have described a sharper rise in LT listings for ALD, now accounting for 40% of all LT in North America, more than NASH and HCV combined.[4,86,94]

Post-transplant survival of selected patients undergoing LT for ALD has shown to be comparable to other indications.[95] Although a return to some degree of alcohol consumption after LT is seen in up to 50% of recipients, only a minority die of complications of alcohol abuse, suggesting that the transplant process adequately selects those committed to long-term abstinence.[96] Yet, health care professionals remain reluctant to refer these patients for formal assessment, and referral occurs in a minority of patients with ALD.[97] Importantly, experts acknowledge that the "6-month rule," as a required duration of pre-LT abstinence, is questionable and not evidence-based, and that decisions on LT candidacy should not be made solely on length of sobriety criterion.[95,98] A better understanding of the management and approach of AUD has led to several changes in the LT setting. Early LT for severe AH has shown encouraging results in highly selected patients.[99-103] In a recent large prospective multicenter Franco-Belgian study that included 3 groups of patients, those with severe AH transplanted, those with AH rejected for LT due to socio-psychological contraindications, and those with alcohol-associated cirrhosis transplanted after a pretransplant abstinence period of at least 6 months, LT was found to significantly improve the survival of patients with severe AH not responding to steroids compared with those rejected for transplantation (83% vs 28% at 2 years).[103] Most importantly, post-transplant survival at 2 years was found to be similar between AH (no mandated period of abstinence) and ALD cirrhosis (with at least 6 months abstinence) groups.[103] A large multicenter retrospective study in the U.S. (ACCELERATE-AH) showed similar survival with use of early LT for severe AH.[102] By accepting this indication, we acknowledge equity of access compared with other similarly "self-inflicted" liver diseases such as NAFLD or paracetamol-induced acute liver failure. In addition, concerns that early LT for AH may decrease donation are not supported by data.[104]

Concerns regarding LT for severe AH relate to 2 major unsolved issues.[105-107] The first is the lack of accurate predictors of outcome, either recovery or death, resulting in transplantation of patients likely to recover with supportive care. Furthermore, uniform criteria may

not be applied in all centers; in fact, the stringent and strict criteria applied in initial experiences in reference centers required a strong infrastructure with multidisciplinary teams, complex evaluation process, and expertise in medical management.[99] The second issue is the difficulty in defining the best outcome measure, whether it be survival or relapse, and differentiating between slip and sustained harmful drinking, as the latter pattern has been associated with reduced survival.[108,109]

To adequately select patients with severe AH for LT, patients should be at substantial risk of fatal outcome in the absence of LT. Several systematic reviews and meta-analyses have demonstrated that corticosteroid therapy reduces 28-day mortality in severe AH as defined by a Maddrey score greater than 32, yet the benefit is lost at 6 months, at which point abstinence becomes the most relevant prognostic factor.[110-115] Overall, patients with severe AH who are left untreated have a 28-day mortality of around 35% to 40%, whereas in those treated, mortality is reduced to 20%,[110,115] with a best opportunity for corticosteroid to be beneficial among those with a MELD score between 25 and 39.[114] Response to steroid therapy is key, allowing null responders to avoid unnecessary adverse events and progress to further therapies including LT. Patients assessed at 4 or 7 days using the Lille score have a very poor outcome if the score is greater than 0.56 (50% 28-day survival), intermediate survival of 79% for partial responders (score between 0.16 and 0.56), and a 91% survival rate for complete responders.[110] Unfortunately, AH prognostic scores that predict the point of no-return need to be improved. In a recent multinational and multicenter study including 2581 patients, the MELD score was shown to be the best tool to predict mortality in AH, and superior to the Maddrey score. Meld-Na did not add value to MELD, and no other variables were associated with mortality.[116]

AUD is a chronic disorder characterized by episodes of remission and relapse. Maintaining alcohol abstinence post-LT is a key factor determining outcome. Several studies have shown that relapse following LT for AH ranges between 10% and 25% within the first 2 to 3 years.[99-103,117] In a recent prospective study, alcohol relapse was detected in 34% at 2 years compared with 25% in those transplanted for alcohol-associated cirrhosis with 6-month abstinence pre-LT. In fact, despite the lack of impact on transplant survival at 2 years, the rate of high alcohol intake was greater in the early transplantation group (22%) than the standard LT group (5%).[103] In a Spanish cohort examining predictors of heavy alcohol relapse after LT in patients with ALD cirrhosis over a 10-year follow-up period, the cumulative incidence of heavy alcohol relapse increased over time from 2.3% at 1 year after transplantation to 29% at 10 years after LT.[118] Several risk scores have been used to date to select patients for LT in the setting of AH, including the High-Risk Alcoholism Relapse (HRAR) tool, the SIPAT (Stanford Integrated Psychosocial assessment for Transplantation) or the SALT (Sustained alcohol use post LT) scores.[118-121] Among other items, these scores include a psychosocial assessment addressing the underlying AUD, social support, psychosocial stability, abuse of other substances, and motivation. These scores though should not be used solely to determine candidacy given their low positive predictive value. Professionals with addiction and transplant experience should be involved in the process and help create treatment plans both in the pre-urgent and post-transplant settings to mitigate risk.[96,122,123] Effective therapies for AUD can be offered after LT.[96,122,123] Thus, although severe AH was formally a contraindication to LT, recent guidelines and societies support this indication in those expected to have a fatal outcome without LT, without contraindications to LT, and who are judged to be suitable candidates to abstain from alcohol. Long-term abstinence should be supported by multidisciplinary teams that incorporate addiction specialists targeting patients for early and continuous interventions.

Transplantation in the Setting of Viremic Donors

An important option to expanding donors is the utilization of donors that previously were discarded or used only in highly select circumstances. Donors with active viral infections of the liver, specifically hepatitis B virus (HBV) and HCV, will effectively transmit those infections to the recipients. However, with the availability of highly effective antiviral therapies, use of these organs can be safely undertaken, although recipients need to be fully informed of potential short- and long-term complications. Access to antiviral therapy is essential. For HCV, therapy is finite, whereas for HBV, indefinite therapy is required. Livers from donors with HCV and HBV need to be evaluated for fibrosis pre-implantation, with use restricted to those with no or minimal levels of fibrosis. Use of organs from HIV-positive and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) donors has been undertaken, representing the most recent expansion of the viremic donors.

Hepatitis C virus. The availability of DAAs, which are well-tolerated and safe in transplant recipients and have high efficacy with short courses of treatment, allowed an expanded use of livers from HCV-infected donors[124] (Table 1). Historically such organs were used only in recipients with chronic HCV infection, but since 2014, this practice has expanded to recipients without HCV infection.[125-127] Use of HCV viremic donors requires access to DAAs post-transplant, with experts favoring treatment immediately or shortly after transplantation,[124] to minimize any direct or indirect effects of viremia in the recipient. Although shorter courses of DAAs have been used in non-liver transplant recipients of HCV-viremic donors, for liver recipients, standard duration of 12 weeks of therapy is typical.[126,127] HCV viremia in the recipient is quantifiable in blood within

the first 1 to 2 days,[126] and elevation of serum aminotransferase levels occur within the first few weeks, with cases of fibrosing cholestatic hepatitis reported. This natural history provides the rationale for early treatment, ideally before clinical manifestations. Efficacy is high with DAAs, with sustained virologic responses reported in >95% with the first course of treatment. Retreatment may be necessary, with the approach similar to that of non-transplant patients, with triple combinations of sofosbuvir-velpatasvir-voxilaprevir or glecaprevir-pibentasavir-sofosbuvir the best choices. Drug-drug interactions need to be considered, and monitoring of drug levels during treatment is prudent, as rapid clearance of HCV viremia under DAA therapy has been associated with acute and chronic rejection.[125,128,129]

Hepatitis B virus. There are 2 types of HBV-infected donors that are being used in LT – those who are anti-HBc positive alone (with or without anti-HBs) and those who are HBsAg-positive (Table 1). The latter group is a more recent development, in part driven by the donor needs in countries with a high prevalence of such donors, such as Asia. Anti-HBc positive donors have been used successfully for decades with the use of anti-viral prophylaxis to prevent reactivation and progressive liver disease. Such donors typically have undetectable or low-level viremia, and if antiviral therapy is initiated at time of transplant, recipient viremia can be prevented. HBV-infected organs are often targeted to recipients who are HBV-infected where anti-viral prophylaxis is routine. Hepatitis B immune globulin has no role in prevention of HBV infection in this setting as the organ is already HBV-infected. The mainstay is indefinite antiviral therapy, with entecavir or tenofovir preferred, due to high efficacy and low risk for viral resistance with long-term use.[130] A systematic review of 19 studies using anti-HBc-positive donors reported de novo infection in 3.4% among HBV-naïve recipients given anti-viral prophylaxis (included use of lamivudine) but found recipients who were anti-HBs positive to have a negligible risk for de novo HBV infection, such that no prophylaxis could be considered.[131]

The use of livers from HBsAg-positive donors is less well-established. An absence of hepatitis D virus (HDV) coinfection is required, as HDV infection cannot be effectively prevented with current antivirals, and HDV infection can be rapidly progressive post-LT.[132,133] Until new HDV therapies are available, HDV in the recipient should be regarded as absolute contraindication to the use of HBsAg-positive organs. Additionally, the presence of HCC in the recipient may be important. Some[134,135] but not all[136] studies show that recipients with HCC who receive an HBsAg-positive donor have lower survival than those receiving HBsAg-negative donors. HBsAg is detectable in serum post-LT,[134,135,137,138] and presence of HBV DNA in some for up to 1 year post-LT on antiviral

Table 1. Viremic Donors and Their Management in Liver Transplant Recipients

Donor status	Pre-LT considerations	Management of recipient infected with same virus	Management of recipient uninfected pre-LT	Additional precautions
HBsAg-negative, anti-HBc positive	Assess severity in fibrosis in donor liver Assess anti-HBs status of recipient	Antiviral therapy from time of LT HBIG may be considered	Antiviral therapy from time of LT No role for HBIG If anti-HBs+, antiviral therapy may not be needed	Antivirals of choice – tenofovir or entecavir (high barrier to resistance)
HBsAg positive	Assess severity in fibrosis in donor liver	Antiviral therapy from time of LT No role for HBIG	Antiviral therapy from time of LT No role for HBIG	Antivirals of choice – tenofovir or entecavir (high barrier to resistance) Avoid in recipient with HCC as indication Consider HCC surveillance post-LT
HCV RNA-positive	Assess severity in fibrosis in donor liver	Antiviral therapy typically given within first year, when clinically stable	Preemptive or early antiviral therapy	Monitor for rejection during and for few months post-DAA therapy
HIV RNA-positive	Conducted under study protocol	Continue ART post-LT, monitor adherence Drug-drug-interactions need attention, particularly with protease-inhibitor inclusive ART	Not recommended	Heightened surveillance for opportunistic infection and cancer

ART, Antiretroviral therapy; DAA, direct-acting antiviral; HBIG, hepatitis B immunoglobulin; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; LT, liver transplantation.

prophylaxis.[138] With adherent patients, this can be anticipated to control viremia and prevent hepatitis and progressive liver disease. With follow-up period of up to 3 to 5 years post-LT, graft and patient survival rates are acceptable in recipients of HBsAg-positive organs compared with HBsAg-negative organs,[134,135,137,138] although larger studies with longer periods of time are needed to fully characterize patient and graft risks. Pending further data, LT programs should carefully weigh the risk-benefit of using HBsAg-positive donors in recipients with HCC and consider surveillance for HCC in all recipients of HBsAg-positive donors.

Human immunodeficiency virus. With the introduction of highly effective antiretroviral therapy in the 1990s, HIV infection became a long-term manageable disease and LT recipients with HIV who receive liver grafts from HIV-uninfected donors have graft and patient survival rates similar to non-HIV infected persons in the current era.[139] The use of HIV-positive donors in the USA was not allowed until 2013 when the HIV Organ Policy Equity act was passed, facilitating use and research in utilizing HIV positive grafts (Table 1). In a prospective multicenter U.S. study where 45 LTs were performed using anti-HIV positive donors (24 HIV donor and recipient positive [D+/R+], 21 HIV donor negative, recipient positive [HIV D−/R+])[140], 1-year graft survival was similar but patient survival lower (83.3% vs 100.0%; $P = .04$), with the D+/R+ group experiencing more opportunistic infections and cancer. Rates of acute rejection at 1 year were similar in D+/R+ vs D−/R+ (10.8% vs 18.2%)[140] and lower that historical cohorts of HCV-infected HIV D−/R+ (39%).[141] A longitudinal study of HIV viremia among 17 LT and kidney transplant recipients (HIV D+/R+) found no evidence of HIV superinfection in antiretroviral therapy-adherent patients.[142] Collectively, these early results are encouraging, but clearly strategies to reduce the patient survival disparity are needed. Barriers to greater use of HIV-positive donors include stigma, low rates of donor registration, and significant anti-HIV false positive rate among tested donors (∼30% among LT donors).[143]

SARS-CoV-2. In a review of U.S. data from March 2020 to August 2021, the proportion of SARS-CoV-2 positive donors increased from 0 to 3.0% (a total over this time of 147 transplants). Although a positive test for viral genome may reflect the noninfectious, convalescent shedding of viral genome, all donors should be treated as infectious. Comparison of 6-month graft survival found no difference in uninfected recipients of donors who were SARS-CoV-2 positive vs negative (97.0% vs 93.9%; $P = .24$).[144] In a systematic review of cases of transplantation from SARS-CoV-2 polymerase chain reaction (PCR)-positive non-lung donors, no instances of SARS-CoV-2 infection were documented in the recipients.[145,146] Use of monoclonal antibodies and antivirals in the donors and/or post-LT as postexposure prophylaxis are most applicable when recipients are SARS-CoV-2-positive.[147] Although the number of cases is quite modest, the positive outcomes with use of livers from SARS-CoV-2-positive donors but low rates of donor utilization, point to a missed opportunity to expand transplant opportunities.

Future Directions in Liver Transplantation

Tolerance and Immunosuppression Withdrawal

Currently, the cornerstone of immunosuppression in LT is calcineurin inhibitors, mainly tacrolimus, associated with mycophenolate mofetil or, less frequently, mTOR inhibitors. These combinations are very effective, and rejection-related graft losses have become very uncommon.[148] However, the downside is that immunosuppression exposure long-life increases the risk for cardiovascular events, malignancies, or chronic kidney diseases.[149] When matching by age and gender, LT recipients have a 2.4-fold higher risk of death and a 5.8-fold higher risk of premature death as compared with the general population.[150] Thus, strategies facilitating reduction or discontinuation of immunosuppression are highly desirable.

The liver is considered a tolerogenic organ.[151] Indeed, LT recipients require lower immunosuppression, and they are at lower risk of acute and chronic rejection as compared to other organ recipients. Interestingly, the liver appears to provide some level of immunological protection for other organ recipients of combined organ transplantation (liver-kidney, liver-heart, or liver-intestine). This immunological benefit is complex and not fully understood but results, in part, in the unique immunologic microenvironment of the liver, which includes a very large vascular bed, and the interactions between parenchymal and immune cells that regulate innate and adaptative immunity and that can promote antigen-specific tolerance.[152]

The feasibility of immunosuppression withdrawal has been known for several decades. Rates of spontaneously tolerant recipients is around 20% to 30%.[153] Importantly, studies were very heterogeneous, including small number of patients, both adults and children, living or deceased donors, and different diseases prior to LT, as well as different time interval between liver transplantation and immunosuppression weaning.[154-156] Theoretically, earlier withdrawal of immunosuppression would be predicted to best minimize the risk of long-term complications, such as renal dysfunction. Patients with recent rejection and those with autoimmune diseases who are at higher risk for rejection should be excluded from withdrawal consideration.[154] Biomarkers to identify those with high likelihood of success with immunosuppression withdrawal and immunomonitoring strategies to assess the safety and success of immunosuppression withdrawal or tolerizing therapies would aid in advancing the field.[157,158] It has been suggested

that the time interval between LT and weaning should be longer than 10 years,[155,156] and older (vs younger) recipients are more likely to become tolerant. However, delaying immunosuppression withdrawal for a decade means a long period of risk to recipients, and thus acceleration of the development of tolerance would be a benefit. Adoption transfer of regulatory T-cell represents an example of new therapeutic strategies focused on enhancement of earlier immune tolerance among LT recipients.[159]

Increasing Donor Organs

Globally, the demand for organs greatly outpaces the supply. The sad consequence of this disparity in organ need vs availability is that many patients die on the waiting list every year. In the U.S., fully 1 of 4 patients who are listed for LT either die on the waitlist (12%) or become too sick to undergo LT (13%).[3] Expanding living donor LT remains a goal in countries where decreased donor LT predominates, such as North America and Europe, but means of increasing the available deceased donors by reducing organ discard rates is another important means of expanding donors (Figure 4).

Machine perfusion of organs from deceased donors. Although patient and graft survival among standard criteria/lower-risk donors is generally above 90% at 1-year post-transplant, graft survival diminishes with higher-risk donors and DCD, which is notably associated with ischemic-type cholangiopathy. Several recent advances in organ preservation through machine perfusion seem poised to considerably enhance organ utilization and outcomes following LT.[160] The standard approach to organ preservation in liver transplantation is by static cold storage. This traditional preservation technique slows graft metabolism, but metabolism never actually ceases. In this regard, dynamic preservation strategies that continuously replenish substrates and remove waste products have gained increasing attention in recent years, including liver graft preconditioning, graft perfusion with hypothermic (HMP) to normothermic machine perfusion (NMP), and systems to improve oxygenation. Techniques of machine perfusion of deceased donor organs can be broadly divided into NMP and HMP. The hypothermic approach can further include oxygen supplementation, delivered through the portal vein only (hypothermic oxygenated machine perfusion [HOPE]) or simultaneously through the hepatic artery and portal vein (dual HOPE). In situ normothermic regional perfusion and combination of the different strategies are increasingly being explored with successful results. Indeed, the ideal perfusion technique might need to combine the benefits of HOPE in reducing cholangiopathy with those of NMP for organ assessment and extending preservation time through a period of controlled oxygenated rewarming in-between.

Emerging potential benefits of machine perfusion include:

- Assessment of graft viability to decide whether or not to proceed with transplantation (eg, through measurement of lactate, pH, glucose, or flavin mononucleotide levels)[161];
- Delipidation of steatotic grafts[162];
- Lower risk of nonanastomotic biliary strictures following DCD.[163]

Thus, while static cold storage performs well for low and average risk donor organs, the capabilities of in situ normothermic regional perfusion, NMP, HMP, and combined strategies seem poised to expand utilization of DCD and extended criteria/high-risk donor organs.

Liver xenotransplantation. Xenotransplantation, transplanting livers from one species to another, has progressed in recent years. Pigs are regarded as the ideal organ donor into humans based on similar solid-organ size match, rapid maturity (reach human size within months), relatively large litter size, and reasonable genetic similarity.[164] With genetic engineering, the pig has been successfully used to provide life-supporting renal

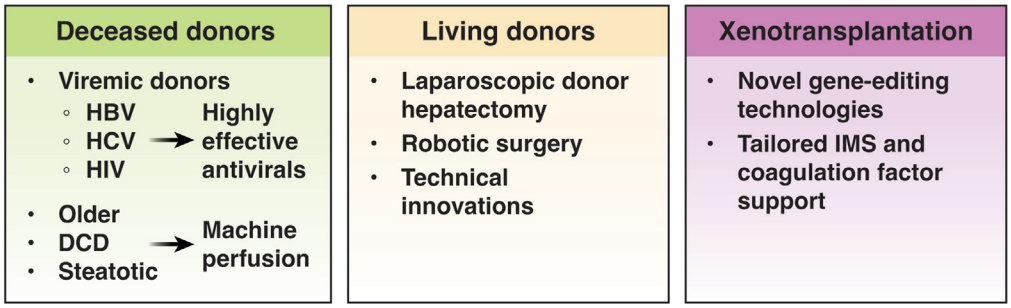

Figure 4. Opportunities to increase donor organs for liver transplantation. Deceased donors remain the primary donor source in many countries, including North America and Western Europe. In these countries, strategies to reduce donor discards due to poor quality are an important focus, and machine perfusion offers great promise. Additionally, using organs from viremic donors is now possible with the use of highly effective antiviral therapies in the recipient. Living donor liver transplant is a dominant form of transplantation in many Asian countries, and innovations that continue to make donation safer and more acceptable include laparoscopic and robotic surgery and other technical innovations. Finally, the final frontier for liver donation is xenotransplantation, which has made considerable progress in recent years but remains elusive. IMS, Immunosuppression.

and heart transplants to non-human primates, but success with liver xenografts has been less, where the longest survival to date with pig to non-human primate LT less than 1 month.[165,166] In January 2022, the first pig-to human heart transplant was undertaken at the University of Maryland; the patient survived 60 days.[167] Pig-to-human renal transplants, using a brain-dead human who was also a deceased organ donor as the model have also been recently reported.[168,169] The main barriers to successful liver xenotransplantation are severe, life-threatening thrombocytopenia and uncontrolled coagulation dysregulation, culminating in lethal hemorrhage.[170] Major breakthroughs in achieving immunocompatibility for cross-species transplant have been achieved by use of novel gene-editing technologies such as CRISPR/Cas-9 that allow genetic knock-outs of highly immunogenic epitopes and engineered knock-ins to allow expression of human transgenes that regulate the coagulation cascade and complement regulatory proteins. Importantly, these genetically engineered pigs have maintained donor viability despite multiple (up to 10)[167] gene knockouts and knock-ins. It is this combination of genetic modifications coupled with tailored immunosuppression and coagulation factor support that offers the best hope for pig-to-human liver xenotransplantation. Of course, animal donor safety and welfare are important, with a need for source animals to be maintained in quarantined, highly monitored settings. Safety and ethical considerations are a major concern, particularly the risk of zoonotic infections with the potential for cross-species infection by retroviruses, which may be latent and lead to disease years after infection. Moreover, new infectious agents may not be readily identifiable with current techniques. Protocols for infection screening, prevention, and risk mitigation are essential to advance the field, as well as plans for lifelong monitoring of recipients of xenografts.[171] Finally, the regulatory processes need to keep pace with scientific advances. The World Health Organization and World Health Assembly have encouraged member states to form regulatory bodies to govern human xenotransplantation studies with the highest standards. In the U.S., the U.S. Food and Drug Administration has provided guidance for xenotransplantation of tissue and organs.[172]

Expanding Indications – Non-hepatocellular Carcinoma Liver Cancer

The success of LT for management of patients with HCC within Milan or UCSF criteria has firmly established this as a therapy for select patients. Similarly, LT achieves acceptable outcomes for selected patients with peri-hilar cholangiocarcinoma (CCA) treated with an approved neoadjuvant chemoradiotherapy protocol and in the U.S., there are established pathways for patients with these malignancies to access LT. More recently, the other primary liver malignancy being considered as potentially suitable for LT is small, intrahepatic CCA (single <2 cm), which is not resectable due to the presence of advanced underlying liver disease. Additionally, there has been expansion of LT for hepatic metastasis, a commonly accepted indication for selected patients with neuro-endocrine tumor but with isolated colorectal metastasis now being explored. Thus, the field of transplant oncology is an exciting future direction – although the ongoing shortage of available donors for these expanded indications may require increased consideration of LDLT as well as techniques to optimize the viability of deceased donor organs which were previously not considered.

In the U.S., the excellent single-center outcomes of neoadjuvant chemoradiation and LT for unresectable perihilar CCA led the United Network of Organ Sharing to offer a standardized MELD exception for this malignancy. Data from 12 U.S. transplant centers (n = 287 patients) showed an intent-to-treat survival at 2 and 5 years after therapy of 68% and 53% and post-transplant, recurrence-free survival rates at 5 years was 65%.[173] Predictors of shorter survival were being outside the United Network of Organ Sharing criteria (those with tumor mass >3 cm, transperitoneal tumor biopsy, or metastatic disease) or with a prior malignancy. Strict adherence to selection criteria is viewed as critical to achieving these outcomes. In comparing wait list dropouts by cancer type, the cumulative incidence rates at 6 and 12 months are 13.2% (95% confidence interval [CI], 10.0%–17.0%) and 23.9% (95% CI, 20.0%–29.0%) for CCA candidates and 7.1% (95% CI, 5.0%–9.0%) and 12.6% (95% CI, 10.0%–15.0%) for HCC candidates.[174] This disparity suggests the need for continuous attention to prioritization policies by cancer type.

Select patients with unresectable, intrahepatic cholangiocarcinoma (iCCA) may derive benefit from LT. In a retrospective, international multicenter cohort of 48 patients found to have iCCA (without HCC) on explant pathology, 31% had "very early" iCCA (single tumor ≤ 2 cm) and 69% had “advanced” iCCA (single tumor >2 cm or multifocal disease). After a median follow-up of 35 months (range, 13.5–76.4 months), the 1-, 3-, and 5-year cumulative risks of recurrence were significantly lower in the very early iCCA group (7%, 18%, and 18%) vs in the advanced iCCA group (30%, 47%, and 61%), and 5-year actuarial survival rates were 65% in the very early iCCA group vs 45% in the advanced iCCA group ($P = .02$).[175] A recent multi-center French study reported outcomes for patients with iCCA <5 cm who underwent LT (n = 49) or liver resection (n = 26) and found that LT had a higher 5-year recurrent-free survival (75% vs.36%; $P = .004$).[176] There are also data from a single U.S. center that has developed a treatment protocol for patients with large, unresectable iCCA typically occurring in the setting of normal liver, without extrahepatic disease or vascular involvement, treated with neoadjuvant chemotherapy (gemcitabine-based) with a minimum of 6 months of radiographic response or

stability before listing for LT.[177] Of 12 patients accepted for LT, 6 underwent LT at a median time of 26 months from diagnosis to LT if, reported overall survival of 100% and 83.3% (95% CI, 27.3%–97.5%) at 1 and 3 years, with 50% (95% CI, 11.1%–80.4%) recurrence-free survival at 3 years.[177] A recent follow-up publication from the same group reported a total of 18 patients with locally advanced iCCA who underwent neoadjuvant therapy plus LT and demonstrated an overall survival at 1-, 3-, and 5-years of 100%, 71%, and 57%, with 7 of 18 (39%) developing recurrence. There are currently 3 registered prospective trials of LT for treatment of either very early iCCA, or large, locally advanced iCCA, which will aid in guiding future patient selection and adjuvant chemotherapy practices.

The international experience with LT for unresectable colorectal liver metastasis (CRLM) is limited. In Norway, investigators undertook the SECA-I study that compared 21 patients transplanted for unresectable CRLM with 47 similar patients treated with first-line chemotherapy, 5-year survival was significantly higher in the LT recipients compared with the chemotherapy group (56% vs 9%; $P < .001$), although the disease-free survival was similar (10 vs 8 months).[178] The tumor characteristics associated with better overall survival were size <5.5 cm, time interval between the diagnosis of the primary and the LT >2 years, carcinoembryonic antigen <80 μg/L, and stability or regression of the metastases on neoadjuvant chemotherapy. In applying these to a risk score (Oslo score with 1 point for each factor), the overall 5-years survival was 75% in the low-risk group (0) vs 0% in the high-risk group (3 or 4).[179] In North America, a recently published multi-center series of 10 patients who underwent LDLT for CRLM noted with 1.5 years of follow up, an overall survival of 100% and a recurrence-free survival of 62%.[180] This study highlights the potential use of LDLT for this indication, where timing of LT is likely important for maximizing success. The rates of recurrence with LT for CRLM are higher than for other oncologic indications for LT. Thus, offering LT for this indication should be under study protocols. Larger studies comparing LT with state-of-the art chemotherapy ($\pm$ locoregional therapy) with longer term follow-up are needed. Prospective studies comparing LT with best palliative chemotherapy are underway (TRANSMET [NCT02597348] from France and SECA-III [NCT03494946] from Norway).

Summary

Liver transplantation has seen significant changes in the past decade, including the expanding use of MELD-based models to prioritize organs (ie, MELD 3.0), the changing indications (reduction of viral-related indications and increase of metabolic-related or cancer-related indications), the changing phenotype of transplant candidates and donors (older, higher frequency of comorbidities, particularly metabolic syndrome, increasing disease severity, and sarcopenia/frailty). Despite increasing complexities, post-transplant outcomes remain good and strategies continue to evolve to reduce surgical complications through enhanced recovery after transplantation programs,[179] minimally invasive donor hepatectomy (laparoscopic or robotic surgery),[180] and donor pool expansion through the safer use of donation after circulatory death in the context of machine perfusion.

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