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The gold standard treatment of end-stage liver disease continues to be liver transplantation (LT). The challenges of LT require skilled anesthesiologists to anticipate physiologic changes associated with end-stage liver disease and surgical considerations that affect multiple organ systems. While on the waiting list, patients may be placed on new anticoagulation medications that can confound already complex coagulopathy in LT patients. Pain management often is an afterthought for such a complex procedure, but appropriate medications can help control pain while limiting opioid medications. Surgical stress and medications for immunosuppression can affect perioperative glucose management in ways that have implications for patient and graft survival. The coronavirus disease 2019 pandemic in 2020 provided a new challenge for anesthesiologists. The uncertainty of the novel respiratory virus challenged providers beyond just LT patients.

LIVER TRANSPLANTATION (LT) continues to be the mainstay of treatment for end-stage liver disease. This review article provides an update from the literature on relevant topics for anesthesiologists caring for LT patients. Coronavirus disease 2019 (COVID-19) challenged all healthcare providers in 2020, and anesthesiologists managing LT patients were no exception. Because the role of anesthesiologists expands into perioperative management, management of anticoagulation medications may require intervention. Pain management for LT patients has intraoperative and postoperative implications. Perioperative glucose management also presents a unique challenge in LT patients, and appropriate management can have effects after LT.

COVID-19 and LT

Near the end of December 2019, people began to develop clinical characteristics of a viral pneumonia in Wuhan, China, which quickly was determined to be a novel coronavirus. This novel coronavirus would become known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the rampant disease it spread is known as COVID-19. In just more than two months from the initial case report, on December 12, 2019, the World Health Organization released a situation report on February 29, 2020, indicating 79,394 confirmed cases of SARS-CoV-2 and that 2,838 deaths had occurred. Of these cases, 6,009 had been confirmed in 53 countries outside of China. It was clear at this time that COVID-19 posed a significant threat to global public health.

SARS-CoV-2 is a -coronavirus, meaning it is a single, positive-stranded RNA virus. On the surface of the virus is an S-glycoprotein, which binds to the human cellular receptor angiotensin-converting enzyme 2 and internalizes the virus. Angiotensin-converting enzyme 2 most commonly is found in the lower respiratory tract and also can be found in biliary and liver epithelial cells, making the liver a potential target for infection. Elevated serum biochemistries, mainly aspartate aminotransferase and alanine aminotransferase, can become elevated in severe cases of COVID-19. Because of these findings, patients with nonalcoholic fatty liver disease (NAFLD) and cirrhosis and post-transplantation patients were considered...
to be at an increased risk for severe COVID-19. In order to avert severe consequences on the transplantation community, organizations involved in LT released recommendations and guidance for LT programs and clinicians moving forward during the COVID-19 pandemic.

As early as February 27, 2019, the Infectious Diseases and Liver Transplantation Special Interest Group of the International Liver Transplant Society released a statement saying that the risk of virus transmission from a donor is low, but present, because SARS-CoV-2 RNA had been identified in the plasma of infected patients. At that time, without rapid testing for COVID-19 readily available, it was recommended to avoid deceased and living organs retrieved from a donor in a high-prevalence area. For LT candidates, it was recommended to avoid a transplant in a patient with developing or active respiratory symptoms and to wait 14 days if a candidate traveled to an area with COVID-19 needed to be a high priority and “prudence suggests that organs from positive donors not be accepted.”

Another drastically important piece of this guidance was that each program needed to assess program-specific risk-benefit analyses on a case-by-case basis. This was because of the significant variance of infection rates throughout the United States at that time. Recommendations were to continue lifesaving and life-altering transplantations and for living donations to be placed on hold, assuming the recipient could wait. As for deceased donors, testing them for COVID-19 needed to be a high priority and “prudence suggests that organs from positive donors not be accepted.” Once hospitalized, it was important to prevent person-to-person transmission; in particular, in the operating room and intensive care unit. Anesthesiologists and intensivists are at a very high risk for exposure because they perform aerosol-generating procedures; therefore, they recommended that transplantation staff undergo proper training with protective gear, including N95 masks.

As the pandemic progressed, the American Association for the Study of Liver Disease released its expert panel consensus statement. Of special interest was the section regarding patients with decompensated cirrhosis and patients on the LT waiting list. They encouraged transplantation centers to continually analyze the burden of COVID-19 locally and how this would affect patients waiting for an LT. At that time, a reduction in organ recovery based on institutional resource limitation was expected, making risk stratification even more important than normal. Many hospitals were instituting the Center for Medicare and Medicaid Services recommendations on limiting nonessential surgeries in order to conserve resources. Transplantation surgery was excluded from this and categorized as tier 3b, which means “do not postpone.” Finally, the experts discussed specifically SARS-CoV-2 in donors and recipients and concluded that donors who test positive are medically ineligible for donation and transplantations should not be performed in positive recipients. All this information was shown in a flow chart for a quick reference guide to decision-making (Fig 1).

With the recommendations now in place from the LT community, programs needed to decide how they would handle transplantations during the pandemic. One of the earliest analysis of the effect COVID-19 had on transplantations in the United States, specifically deceased donor LT (DDLT), compared data from February—March 2019 with data from February—March 2020. The analysis found an 11% decrease in deceased donors for all organs during this timeframe, which resulted in a 24.7% decrease in adult DDLTs nationally. A questionnaire to determine the effect of COVID-19 on all solid organ donations, comparing March—May 2019 with March—May 2020, was conducted with 17 organ procurement organizations in the United States and Puerto Rico. This survey showed an 11% decrease in organ authorization by donor families, a 17% decrease in total number of organs recovered, and an 18% decrease in the total number of organs transplanted in the 90-day period. Contributors to this decline, as found in another survey, included suspensions and restrictions of certain transplantation programs, such as living donor kidneys and livers and DDLT. This decline in donation and transplantation early on in the pandemic reiterated the uneasiness shared by the LT community in regard to those awaiting transplantation.

The potential decline in transplantation warranted clinicians in the community to consider using organs from COVID-19—positive donors in order to maximize all possible deceased donor organs. The argument being patients with a significantly high Model for End-Stage Liver Disease score (≥40) may have a better clinical outcome if they received an organ from a SARS-CoV-2—positive donor because of a high likelihood of death without transplantation. Utilization of livers from SARS-CoV-2—positive donors was believed to be dangerous by most others because of hepatocellular injury of patients with COVID-19, possible direct viral infection of the liver, and first-pass absorption through the gut. A literature review showed that no known SARS-CoV-2 donors were used for LT in the United States. There have been multiple case reports of SARS-CoV-2—positive recipients undergoing LT after resolution of symptoms or negative tests, with good outcomes.

A more comprehensive analysis was performed later in the pandemic to better understand the effect of COVID-19 on LT in the United States. This study used the Scientific Registry of Transplant Recipients to compare waitlist registrations, waitlist mortality, and DDLTs from March—August 2020 to expected values based on trends from January 2016—January 2020. They also investigated local COVID-19 incidence at the state and center level to provide further insight on the effect of COVID-19. In states with the highest COVID-19 incidence from March 15—April 30, there were 33% fewer new listings, 59% more waitlist deaths, and 34% fewer DDLTs than expected. However, states with the lowest COVID-19 incidence during this timeframe had no change in new listings or DDLTs. Using the guidelines and recommendations by multiple national societies, August waitlist outcomes were
occurring at the rates seen in previous years and DDLTs actually were occurring 13% more frequently compared to previous year across all states. In a matter of months, the transplantation community had adjusted its focus on the pandemic, instituted changes to improve patient care, and nearly normalized LT practice throughout the United States.

COVID-19 has had a variable effect on LT in the United States. Local COVID-19 hospitalizations altered the ability to safely care for critically ill COVID-19 patients in addition to post-LT patients. However, some centers, including the authors’ institution, saw an increase in transplantations in 2020 for reasons that are not clear to the authors of the present review. Recognition should be given to the various organizations and societies because their recommendations aided in the continuation of transplantations during this time and inevitably saved numerous lives via LT. As the pandemic continues to progress, so does the knowledge of the disease and the best way to handle it. Research related to the full effect of COVID-19 on LT will be of interest in years to come.

Direct Oral Anticoagulants in LT Patients

Hemostasis in patients with liver disease is a delicate balance because these patients exhibit both hypercoagulable and hypocoaguable properties. Previously, cirrhotic patients were believed to be “autoanticoagulated” because of their decreased production of clotting factors, elevated international normalized ratio, thrombocytopenia, and platelet dysfunction. Clinically significant bleeding continues to be the prevailing concern, although excessive clot formation also has been recognized as an important issue in these patients. Atrial fibrillation (AF) is the most common cardiac arrhythmia, and its incidence increases with age. In addition, the risk of venous thromboembolism (VTE) and portal vein thrombosis (PVT) contribute to morbidity in older patients. Because older patients are listed for LT, these comorbidities are more common. A meta-analysis by Ambrosino et al. suggested that cirrhotic patients demonstrate a 1.7-fold increased risk for VTE and noted a higher prevalence in males. They suggested that cirrhosis was an independent risk factor for VTE. In addition, Lee et al. denoted a 1.5-fold increase in AF in the
cirrhotic patient population. Currently, there are no specific consensus guidelines for the treatment and prevention of VTE in patients with advanced liver disease. Traditionally, patients with advanced liver disease were treated with vitamin K antagonists (VKAs) or low-molecular-weight heparin (LMWH) because of their low cost, physician experience with these medications, and reversibility. Nonetheless, VKAs and LMWH have not become a mainstay of prevention because of altered pharmacokinetics and pharmacodynamics, decreased plasma levels of proteins C and S further augmenting pharmacologic efficacy, dietary restrictions with warfarin, and the implicit difficulty in monitoring VKA effectiveness in patients with an abnormal international normalized ratio.

Direct oral anticoagulants (DOACs) are recommended over VKAs, when appropriate, as the current treatment modality for both VTE and AF in the general population. These medications have not been studied extensively in patients with advanced liver disease; Child-Turcotte-Pugh C patients initially were excluded from phase III trials. Advantages of DOACs include oral administration (compared with LMWH), similar efficacy, predictable mechanism of action independent of antithrombin levels, standard dosing schedules, and no required monitoring.

A meta-analysis of 152,116 patients from phase III randomized controlled trials for DOACs, demonstrated that DOACs were not associated with increased risk of drug-induced liver injury in the general population. Another study in 2017 assessed more than 113,717 patients with nonvalvular AF and found that DOACs were associated with lower rates of hepatic injury hospitalization compared with VKAs (warfarin). Dabi-gatran demonstrated the lowest risk for hepatic injury among this population. Neither of these meta-analyses included patients with advanced liver disease, although based on more recent retrospective findings, pharmacologic effects potentially may be extrapolated to the cirrhotic population. A 2013 randomized double-blinded, double-dummy trial compared the DOAC edoxaban with warfarin in AF patients, with the primary efficacy endpoint of stroke or systemic thrombus and a primary safety endpoint of major bleeding. Of the 21,105 patients enrolled in this study, 1,083 (5.1%) had a history of mild liver disease. Patients with liver disease had a known increased risk of bleeding; however, there were no differences in the efficacy or safety of edoxaban compared with warfarin in patients in this subgroup. In addition, there were no significant differences in liver-related adverse events.

Patients with advanced liver disease primarily were excluded from randomized controlled trials because of potential risk of bleeding, but emerging retrospective research has demonstrated that DOACs have comparable or lower rates of bleeding in cirrhotic patients when directly compared with standard therapies. A number of systematic reviews and meta-analyses have proposed similar safety and efficacy profiles. Mort et al. found a comparable annualized bleeding rate in cirrhotic patients taking DOACs to cirrhotic patients on VKAs. These rates were analogous to previously published rates in patients without cirrhosis who were prescribed DOACs. Findings from Davis et al. corroborated the safe use of DOACs in advanced liver failure, as evidenced by a similar incidence of major bleeding events when compared directly with warfarin. This retrospective study did comment that the enrolled patients on DOACs were preferentially more likely to have mild liver disease. A retrospective cohort study demonstrated that DOACs were safer and more effective than warfarin in AF patients with liver disease. DOACs were associated with lower risk of ischemic stroke, intracranial hemorrhage, gastrointestinal bleeding, major bleeding events, and all causes of death. These results were consistent across the subgroup of participants who were noted to have significant active liver disease. Several meta-analyses of retrospective studies have demonstrated comparable safety and efficacy profiles between DOACs and VKAs, but there is difficulty applying these data to patients with severe or end-stage liver disease. Even though the retrospective data are promising, there remains a lack of prospective studies.

PVT is recognized problem for patients awaiting or undergoing LT, occurring in up to 20% of patients with cirrhosis. Both meta-analyses and retrospective studies have demonstrated the safety and efficacy of LMWH and VKA treatment for PVT. A prospective study assessed the safety and efficacy of DOACs for treatment of VTE of atypical locations, with the most common location being the portal vein (29/63 patients). Rate of thrombosis recurrence and rate of clinically relevant bleeding were similar to previously published data for patients treated with LMWH or VKAs. Hepatic function may decline over time in patients with PVT; possibly changing the anticoagulation effect of DOACs without notice because no routine monitoring is recommended. PVT is associated with mesenteric vein thrombosis, which potentially can cause impaired drug absorption and decrease the efficacy of DOACs. A 2018 meta-analysis of 17 studies compared treatment response, bleeding, and anticoagulation modalities in cirrhotic patients with PVT. Pool rates of bleeding were similar among groups treated with LMWH, VKA, or DOACs. Uniquely, this study used meta-regression analysis to assess effect based on the patient’s CTP (Child-Turcotte-Pugh) classification and found that the severity of disease did not appear to influence outcomes. The role of DOACs in patients with liver disease has not been discretely defined, but recent literature supports their use as an effective and safe treatment in this patient population.

Post-LT complications from thromboembolic events can negatively affect patient and organ outcomes. Thrombotic events occur in 2%-to-11% of patients after LT. A small retrospective study associated DOACs with less bleeding risk when postoperative transplantation patients were matched with warfarin-treated control patients. Although anticoagulation selection should continue to depend on specific patient factors, including renal function, drug-drug interactions, and insurance coverage, DOACs appear to be safe for use in cirrhotic patients before and after transplantation.

A national survey of organ transplantation programs in 2019 suggested that DOACs are being prescribed with the perception that they pose a similar bleeding risk to traditional VTE anticoagulation. Apixaban was the
anticoagulation medication most commonly prescribed for patients on the transplantation waitlist. DOAC reversal agent use before transplantation was noted to be uncommon, primarily occurring before thoracic organ transplantation. As illustrated by Vuilleumier et al., management of DOAC-related bleeding during LT may be burdensome, but reversal agents for DOACs as noted in Table 1 may prove to be truly valuable tools. Guidelines published in the American Journal of Hematology (2019) recommended that prothrombin complex concentrates be used for treatment of life-threatening bleeding when reversal agents are unavailable.

**Pain Management in LT**

Pain can be a divisive issue in LT patients. It can be argued that LT is among the most extensive abdominal surgeries in terms of duration and stress for the patient, with the large abdominal incision and the use of multiple retractors, which contribute to postoperative pain. Despite these factors, postoperative pain after LT has been shown to be not as severe compared with open cholecystectomy or hepatic resection. Even though the administration of opioids intraoperatively and postoperatively has long been considered a viable option, the opioid epidemic has forced clinicians to revisit their approach to perioperative pain management. The new approach to a comprehensive analgesic plan should have the aim of improving respiratory function, aiding in early mobilization, and accelerating postoperative recovery with limited opioid consumption.

In the context of this epidemic, combined with the prevalence of substance use disorders among LT recipients, more thought should be given to the implementation of multimodal pain management regimens in an effort to reduce perioperative opioid use after LT. In fact, multimodal analgesic approaches have resulted in reduced opioid use in LT recipient populations. Determining what non-opioid agents a provider can use in LT patients can be a challenge. A recent review of multimodal analgesics for LT patients provides an evidence-based approach to pain management. The authors recommendations are listed in Table 2. Even though most therapies are familiar to anesthesiologists, the evidence remains limited on their utility in LT patients. Even with limited data, Kutzler et al. sought to investigate the development of a comprehensive multidisciplinary opioid avoidance pathway (OAP) for LT recipients at their institution. The OAP was developed by a multidisciplinary team of healthcare specialists and is offered to all LT recipients regardless of substance use history. Table 3 illustrates the general pathway for patients from pre-transplantation to post-transplantation care. Ultimately, they found that this pathway reduced morphine milligram equivalents by 92% per postoperative day, with no difference in length of stay compared with historic cohorts. This difference was most pronounced in the first five postoperative days. Of note, two patients in the OAP group used zero opioids during their admission. Their approach was able to provide an analgesic regimen that effectively reduced inpatient and outpatient opioid use.

Opioid-sparing techniques are used in many surgeries and can play a critical role in pain management for LT patients because opioids may have negative consequences in end-stage liver disease because of alterations of liver function and drug pharmacokinetics. The majority of opioid metabolism is liver-dependent, and the extent of liver disease can have a significant effect on this metabolism. Furthermore, hypoalbuminemia, common in LT patients, causes free drug concentration to increase, resulting in enhanced distribution and higher concentration of drug at the site of action. End-stage liver disease patients also may exhibit an increased density and affinity of central mu-opioid receptors in the brain, contributing to the increased sensitivity to opiate agonists in such populations. In addition, opioids may precipitate or aggravate hepatic encephalopathy.

Commonly used opioids in LT, fentanyl and sufentanil, are extensively metabolized by the liver. Fentanyl, a synthetic opioid analgesic, has a high hepatic extraction ratio and is highly protein-bound, largely to albumin. Clearance of fentanyl is determined by hepatic blood flow and high hepatic extraction of fentanyl, and anesthesiologists should be cognizant that an abrupt increase in plasma fentanyl concentration is observed during the anhepatic phase. Furthermore, an opposite abrupt decrease in the plasma fentanyl concentration is observed during the neohepatic phase. Redistribution largely is responsible for the duration of action of fentanyl after single bolus doses, whereas hepatic elimination is more responsible.
Glucose Management in LT

Hyperglycemia in the perioperative period commonly occurs as a result of critical illness, surgical stress, and medication administration. There remain deleterious effects of hyperglycemia in surgical patients that include but are not limited to increased mortality, increased wound infection rates, and risk factors for postoperative pneumonia and acute kidney injury (AKI).75-77 Management of blood glucose (BG) in LT can be challenging given the significant surgical stress and delivery of large doses of steroids. What effects hyperglycemia has on long-term outcomes remain unclear, with recently published new evidence. In addition, the development of diabetes mellitus (DM) after transplantation is uncommon and anesthesiologists should be aware of the effect this has on cardiovascular function and overall survival.

Early research into glycemic control in LT has been ongoing for years, albeit retrospectively. Building on intensive care data on BG control,78 Ammori et al. reviewed 184 patients who underwent LT to compare outcomes regarding mean BG levels.79 They found a lower rate of infections in the first 30 days for the tighter BG group (mean BG <150 mg/dL) and improved survival at one year and two years. In 2010, Wallia et al. retrospectively reviewed 113 LT and 31 liver-kidney transplantation patients to examine the role of BG control on LT outcomes.80 They found rejection to be more common if a patient’s mean BG during the hospitalization was >200 mg/dL than if the mean BG was <200 mg/dL. Interestingly, the incidence of prolonged ventilation was greater in the lower BG arm for reasons that were not clear to the authors.

Recently, a prospective, randomized, controlled trial examined glucose control for LT patients at a single institution,
comparing strict BG control versus conventional BG control.\textsuperscript{81} Strict BG control was defined as 80-to-120 mg/dL, and conventional control was defined as a BG of 180-to-200 mg/dL. The primary outcomes measured were patient and graft survival at one year. At one year, overall survival was not statistically different (88% v 88%; \( p = 0.999 \)) and there was no difference at three years (86% v 84%; \( p = 0.999 \)) or five years (82% v 78%; \( p = 0.617 \)). Rates of complications (bile leak, bile stricture, cerebral vascular accident, major cardiac event, redo surgery, and wound dehiscence) were similar between both groups. Clinically, the strict control group required more insulin (24.4 U on average) compared with the conventional group (10.0 U). Hypoglycemic events (defined as BG <70 g/dL) were more common in the strict group but not statistically significant.

Postoperative AKI is common in LT patients, affecting 17%-to-95% of patients.\textsuperscript{82} However, the effect of BG on AKI is not well-understood for LT patients. Yoo et al. used time-weighted average glucose levels to evaluate whether poor glucose control was associated with AKI. Their retrospective study grouped patients into four categories based on glucose levels and different quartiles based on the variability of BG levels through 48 hours. Postoperative AKI occurred in 43.1% of patients overall.\textsuperscript{83} Patients in the third and fourth quartiles for BG control were at higher risk for AKI. The authors suggested that glucose variability, rather than hyperglycemia alone, may be a risk factor for postoperative AKI, although additional prospective studies may be helpful.

Development of post-transplantation DM (PTDM) occurs in 12%-to-45% of patients who undergo LT.\textsuperscript{84} With an increasing number of patients who are undergoing LT for NAFLD, the effects of PTDM in patients in these patients are not well-understood. A review of 415 patients focused on graft steatosis, rejection, and patient survival as it relates to PTDM. Rates of PTDM were 34.7%, 46.9%, and 56.2% at one, three, and five years, respectively.\textsuperscript{85} Notably, half the cases of PTDM developed by six months, with 75% by 12 months, indicating a rapid onset after transplantation. Rejection was higher in the PTDM group (31.9%) than in the non-PTDM group (21.8%).\textsuperscript{86}

Indeed, these findings were consistent with early findings that PTDM after LT showed worse patient and graft survival.\textsuperscript{87} Roccaro et al. examined whether the development of PTDM affected the risk of major cardiovascular events (MCE) after transplantation. In a review of 994 patients, they found an overall rate of MCE of 12%.\textsuperscript{88} The incidence of MCE was highest among the sustained PTDM group (18.7%). The risk of MCE was greater in the sustained PTDM group than either the pre-LT DM group or transient PTDM group.

In addition to the development of DM after LT, presenting for LT with preexisting DM carries risk. Long-term follow-up of LT patients with a median of 14 years found that pre-transplantation DM independently predicted atherosclerotic vascular events (AVE).\textsuperscript{89} AVE was defined as specific conditions with evidence of atherosclerotic disease as follows: myocardial infarction, angina, transient ischemic attack, stroke, and intermittent claudication. The authors also noted that pre-transplantation DM doubled the risk for AVE. As discussed in their article, identifying patients with DM may help further risk-stratify them before transplantation.

Even patients without DM are at risk for hyperglycemia after LT given the surgical stress and administration of medications such as methylprednisolone and calcineurin inhibitors. With the risks of hyperglycemia on outcomes and the risk of the development of DM post-transplantation, intervention may prevent long-term complications. In this single-center trial, patients were assigned to different glucose control regimens (<140 mg/dL v <180 mg/dL).\textsuperscript{90} Postoperative glucose readings were followed and noted when >200 mg/dL. Based on the study findings, the following four factors were noted to predict early hyperglycemia after LT: shorter length of stay, use of glucose-lowering medications at discharge, donor female sex, and donor white race.\textsuperscript{91} Even though limited by a single center’s data, this study may prove useful in identifying patients at risk for postoperative hyperglycemia and DM.

Previous retrospective data on perioperative hyperglycemia indicated risks to patient and graft survival. However, more recent data suggest that tight glucose control may not be as essential as previously believed. That said, it is known that the development of PTDM and metabolic syndrome after LT is common and may predispose patients to cardiovascular events.\textsuperscript{92} With NAFLD continuing to increase as an indication for LT, more may need to be done to identify how best to manage perioperative glucose levels. Additional studies are needed to evaluate the effects perioperative glucose management on outcomes and what, if any, interventions can improve both short- and long-term outcomes.

Conclusion

LT anesthesiologists manage complex patients before, during, and after a complex procedure. The unique challenges of end-stage liver disease patients extend to multiple organ systems and require vigilance to manage. The COVID-19 pandemic has presented new challenges to providers, not only to protect their patients but to protect themselves. While managing limited resources early in the pandemic, the concern of limiting life-saving transplantations was a real concern. However, useful guidance from national transplantation organizations proved invaluable in navigating the new normal of COVID-19.

The use of DOACs may provide patients with a better side-effect profile for patients at risk for forming new clots or treating existing clot burden. Understanding how to manage these medications and recognizing the role that reversal agents play and the risk of bleeding are critical for transplantation anesthesiologists. Opioids have long been the mainstay of pain management for surgery, including for LT patients. Their use is not without challenges because long-term use may lead to worse clinical outcomes. Multimodal analgesia seeks to limit opioid use by using many non-opioid medications, but they may have limitations in end-stage liver disease. Finally, the consequences of hyperglycemia during LT may be trivial, especially compared with the long-term of effects of DM after transplantation.
Conflict of Interest

The authors have no conflict of interests to disclose.

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