Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review Article

2020 Clinical Update in Liver Transplantation

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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.

Key Words: liver transplantation; end-stage liver disease; anesthesiologists; coronavirus disease 2019; COVID-19; pain management; anticoagulation; diabetes mellitus

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.[1] 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.[2] Of these cases, 6,009 had been confirmed in 53 countries outside of China.[2] It was clear at this time that COVID-19 posed a significant threat to global public health.[3]

SARS-CoV-2 is a -coronavirus, meaning it is a single, positive-stranded RNA virus.[4] 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.[5] 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.[4,6] Elevated serum biochemistries, mainly aspartate aminotransferase and alanine aminotransferase, can become elevated in severe cases of COVID-19.[6] Because of these findings, patients with nonalcoholic fatty liver disease (NAFLD) and cirrhosis and post-transplantation patients were considered

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to be at an increased risk for severe COVID-19.[6,7] 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.[8]

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.[9] 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.[9] 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 through a high-prevalence area.[9] In late March 2019, the American Society of Transplant Surgeons released initial guidance from their COVID-19 Strike Force. At the forefront was inclusion of social distancing, hand sanitization, and respiratory precautions to be incorporated in all transplantation protocols.[10] 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.[10] 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.[10] 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."[10] 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[4]; therefore, they recommended that transplantation staff undergo proper training with protective gear, including N95 masks.[10]

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.[6] At that time, a reduction in organ recovery based on institutional resource limitation was expected, making risk stratification even more important than normal.[6] 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."[6] 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.[6] 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.[11] 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.[11] 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.[12] 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.[12] 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.[13] 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.[6]

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.[14] 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.[14] 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.[15] 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.[16-19]

A more comprehensive analysis was performed later in the pandemic to better understand the effect of COVID-19 on LT in the United States.[20] 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.[20] However, states with the lowest COVID-19 incidence during this timeframe had no change in new listings or DDLTs.[20] Using the guidelines and recommendations by multiple national societies, August waitlist outcomes were

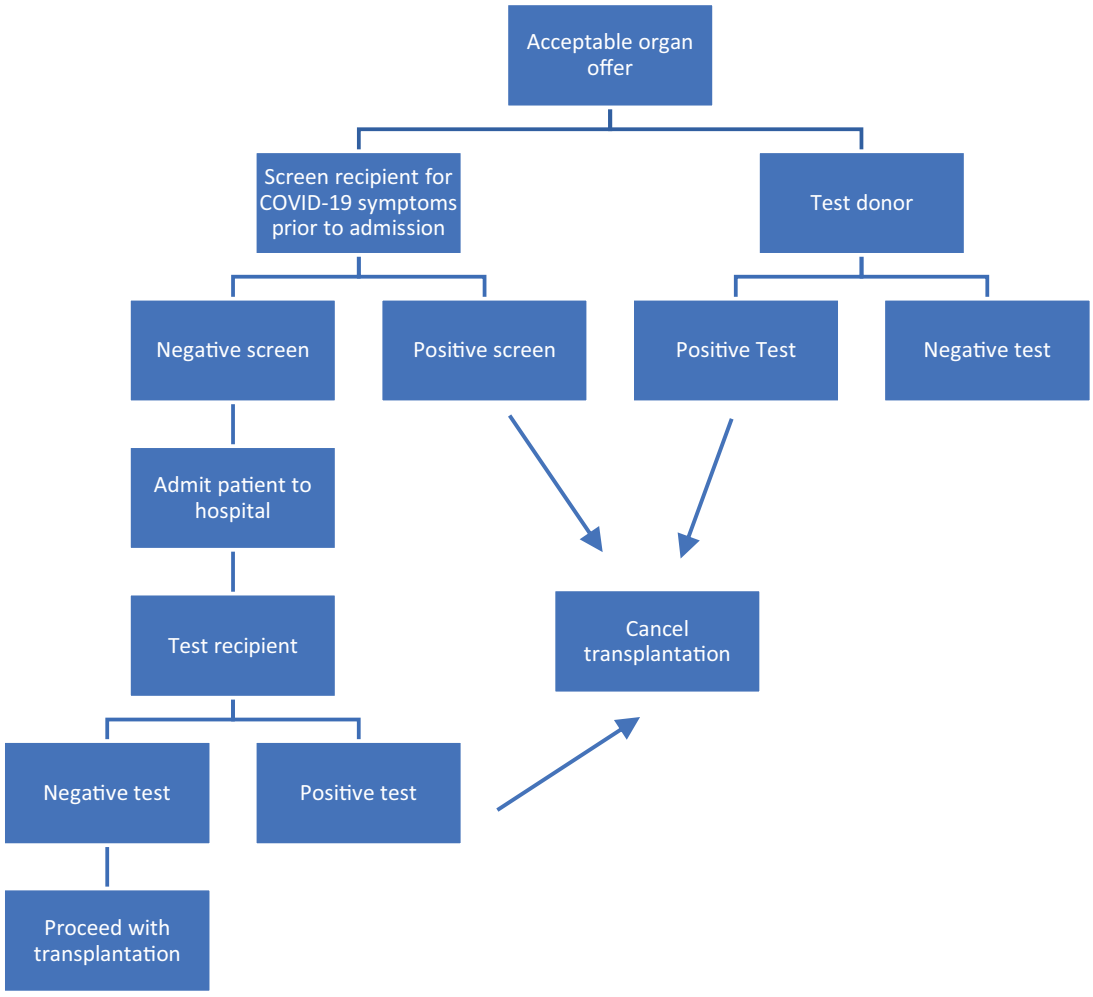

Fig 1. Approach to liver transplantation organ offers.[6,10]

occurring at the rates seen in previous years and DDLTs actually were occurring 13% more frequently compared to previous year across all states.[20] 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.[21,22] Previously, cirrhotic patients were believed to be "autoanticoagulated" because of their decreased production of clotting factors, elevated international normalized ratio, thrombocytopenia, and platelet dysfunction.[23] Clinically significant bleeding continues to be the prevailing concern, although excessive clot formation also has been recognized as an important issue in these patients.[24] 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.[25,26] 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.[27] In addition, Lee et al. denoted a 1.5-fold increase in AF in the

cirrhotic patient population.[28] Currently, there are no specific consensus guidelines for the treatment and prevention of VTE in patients with advanced liver disease.[29] Traditionally, patients with advanced liver disease were treated with vitamin K antagonists (VKA) or low-molecular–weight heparin (LMWH) because of their low cost, physician experience with these medications, and reversibility.[30-32] 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.[33]

Direct oral anticoagulants (DOACs) are recommended over VKAs, when appropriate, as the current treatment modality for both VTE and AF in the general population.[34,35] 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.[32,36] 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.[37]

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.[38] 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). Dabigatran demonstrated the lowest risk for hepatic injury among this population.[38,39] 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.[40] 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.[41]

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.[23] A number of systematic reviews and meta-analyses have proposed similar safety and efficacy profiles.[26,42–44] 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.[36] 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.[32] A retrospective cohort study demonstrated that DOACs were safer and more effective than warfarin in AF patients with liver disease.[45] 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.[28] 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.[29] Even though the retrospective data are promising, there remains a lack of prospective studies.[46,47]

PVT is recognized problem for patients awaiting or undergoing LT, occurring in up to 20% of patients with cirrhosis.[31] Both meta-analyses and retrospective studies have demonstrated the safety and efficacy of LMWH and VKA treatment for PVT.[48] 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.[49] 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.[50] 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. Pooled 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.[51] 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.[50] Thrombotic events occur in 2%-to-11% of patients after LT.[52] A small retrospective study associated DOACs with less bleeding risk when postoperative transplantation patients were matched with warfarin-treated control patients.[53] 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

Table 1
Direct Oral Anticoagulants with Reversal Agents[56]

Direct Oral Anticoagulant	Mechanism of Action	Reversal Agent
Apixaban (Eliquis)	Factor Xa inhibitor	Andexanet alfa (Andexxa)
Dabigatran (Pradaxa)	Direct thrombin inhibitor	Idarucizumab (Praxbind)
Edoxaban (Savaysa)	Factor Xa inhibitor	No reversal agent
Rivaroxaban (Xarelto)	Factor Xa inhibitor	Andexanet alfa (Andexxa)

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.[54] 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.[55] 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.[56]

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.[57] Despite these factors, postoperative pain after LT has been shown to be not as severe compared with open cholecystectomy or hepatic resection.[58,59] 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.[60] In fact, multimodal analgesic approaches have resulted in reduced opioid use in LT recipient populations.[61] 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.[61] Even with limited data, Kutzler et al. sought to investigate the development of a

Table 2
Multimodal Analgesic Agents for Liver Transplantation Patients[61]

	Examples	Evidence-Based Recommendation
Acetaminophen	NA	Level IIIB
NSAIDs	Ibuprofen, ketorolac, celecoxib	No recommendation
Gabapentinoids	Gabapentin, pregabalin	No recommendation
Ketamine	NA	No recommendation
Lidocaine (infusion)	NA	No recommendation
Neuraxial analgesia	Epidural, paravertebral, intrathecal opioids	No recommendation
Fascial plane blocks	Transverse abdominis plane block	Level IIb C

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

comprehensive multidisciplinary opioid avoidance pathway (OAP) for LT recipients at their institution.[62] 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.[62] 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.[63] 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.[64] In addition, opioids may precipitate or aggravate hepatic encephalopathy.[65]

Commonly used opioids in LT, fentanyl and sufentanil, are extensively metabolized by the liver.[66] Fentanyl, a synthetic opioid analgesic, has a high hepatic extraction ratio and is highly protein-bound, largely to albumin.[65] 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.[65] Redistribution largely is responsible for the duration of action of fentanyl after single bolus doses, whereas hepatic elimination is more responsible

Table 3
Suggested Medications from the Opioid Avoidance Pathway[62]

Medication	Preoperative	Intraoperative	Postoperative
Acetaminophen	No	No	Yes
Gabapentin	Yes	No	Yes, adjust for renal function
Ketamine infusion	No	Yes, infusion per anesthesiologist discretion	Continue IV infusion in ICU, sublingual on floor
Opioids	No	Minimize fentanyl use	Non-IV opioids as first line: 1 Tramadol 2 Buprenorphine 3 Morphine IV options: 1 Buprenorphine 2 Morphine
Regional anesthesia	No	Incisional catheters with ropivacaine infusion	Continue postoperatively

Abbreviations: ICU, intensive care unit; IV, intravenous.

for the duration of action with continuous infusions of fentanyl. Continuous infusions should be used with great caution so as not to result in oversedation or prolonged postoperative mechanical ventilation. Because fentanyl is largely devoid of histamine-releasing properties, it may be preferred in the setting of hemodynamic instability.[58] Sufentanil has high hepatic extraction and relevant extrahepatic elimination.[67] A minimal increase in sufentanil drug concentration during the anhepatic phase is suspected. Despite sufentanil relying on partial extrahepatic metabolism, its use in end-stage liver disease patients still requires close attention because its analgesic potency is greater than that of fentanyl, with more immediate respiratory depression and bradycardia. It has been reported that sufentanil produces shorter-lasting respiratory depression and longer-lasting analgesia compared with fentanyl.[68] Hypotension is a well-described effect seen with sufentanil and appears to be dose-dependent and affected by the degree of volume depletion, the latter being a critical consideration in the setting of LT.

In addition to the considerations of acute pain in LT patients, the effect of chronic pain among LT patients is not well-studied. Madan et al. highlighted the common occurrence of chronic pain among LT candidates and its relative undertreatment.[69] Opioid prescribing has increased significantly, and excessive opioid prescribing is prevalent, particularly after surgical care.[70] LT patients represent a population vulnerable to opioid exposure given the prevalence of substance use disorders and the associated risk of opioid misuse.[71] Indeed, a recent review of opioid use while on the transplantation waiting list and after transplantation revealed concerning trends. Higher opioid use while on the waiting list was associated with higher mortality and graft failure rates than that of non-opioid users.[72] Interestingly, the use of opioids had no effect within the first year after LT. Recently, the use of opioids while on the waiting list was shown to increase the risk for development of chronic post-surgical pain.[73] That study of LT patients found 18.9% were on opioids before LT and those patients had higher opioid consumption at 24 hours and seven days after surgery. Furthermore, the development of chronic post-surgical pain was more common in the opioid group.

Pain management for LT patients requires thoughtful preparation and planning, and anesthesiologists are well-suited to help in this process. Early identification of patients on opioids at listing allows for consideration of opioidweaning before transplantation.[74] Use of multimodal analgesia medications dosed to account for end-organ dysfunction associated with end-stage liver disease is essential. Use of regional anesthesia also should be considered in LT patients as an opioid-sparing option. Anesthesiologists should continue to lead future research into which therapies are most beneficial for LT patients.

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.[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 conventical 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.[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.[5] 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.[83] 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.[84] 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%).[84]

Indeed, these findings were consistent with early findings that PTDM after LT showed worse patient and graft survival.[85] 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%.[86] 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).[87] 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).[88] 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.[88] 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.[89] 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.

References

1 Wang L, Wang Y, Ye D, et al. Review of the 2019 novel coronavirus (SARS-CoV-2) based on current evidence. Int J Antimicrob Agents 2020;55:105948.
2 World Health Organization. Coronavirus disease 2019 (COVID-19) situation report −40. Available at: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200229-sitrep-40-covid-19.pdf?sfvrsn=849d0665_2. Accessed January 25, 2021.
3 Cavallo JL, Donoho DA, Forman HP. Hospital capacity and operations in the coronavirus disease 2019 (COVID-19) pandemic-planning for the Nth patient. Available at: https://jamanetwork.com/channels/health-forum/full-article/2763353. Accessed January 25, 2021.
4 Ludwig S, Zarbock A. Coronavirus and SARS-CoV-2: A brief overview. Anesth Analg 2020;131:93–6.
5 Lan J, Ge J, Shan S, et al. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. Nature 2020;581:215–20.
6 Fix OK, Hameed B, Fontana RJ, et al. Clinical best practice advice for hepatology and liver transplant providers during the COVID-19 pandemic: AASLD Expert Panel consensus statement. Hepatology 2020;72:287–304.
7 Ji D, Qin E, Xu J, et al. Non-alcoholic fatty liver diseases in patients with COVID-19: A retrospective study. J Hepatol 2020;73:451–3.
8 Michaels MG, La Hoz RM, Danzinger-Isakov L, et al. Coronavirus disease 2019: Implications of emerging infections for transplantation. Am J Transplant 2020;20:1768–72.
9 International Liver Transplantation Society. COVID-19 statement from the Infectious Disease and Transplantation SIG. Available at: https://ilts.org/covid-19-statement-from-the-infectious-diseases-and-liver-transplantation-sig/. Accessed January 25, 2021.
10 American Society of Transplant Surgeons. ASTS COVID 19 Strike Force guidance to members on the evolving pandemic. Available at: https://asts.org/advocacy/covid-19-resources/asts-covid-19-strike-force/asts-covid-19-strike-force-initial-guidance#.YA7rmelKjWQ. Accessed January 25, 2021.
11 Agopian V, Verna E, Goldberg D. Changes in liver transplant center practice in response to coronavirus disease 2019: Unmasking dramatic center-level variability. Liver Transpl 2020;26:1052–5.
12 Ahmed O, Brockmeier D, Lee K, et al. Organ donation during the COVID-19 pandemic. Am J Transplant 2020;20:3081–8.
13 Boyarsky BJ, Chiang TP, Werbel WA, et al. Early impact of COVID-19 on transplant center practices and policies in the United States. Am J Transplant 2020;20:1809–18.
14 Kates OS, Fisher CE, Rakita RM, et al. Emerging evidence to support not always "just saying no" to SARS-CoV-2 positive donors. Am J Transplant 2020;20:3261–2.
15 Shah MB, Lynch RJ, El-Haddah H, et al. Utilization of deceased donors during a pandemic: Argument against using SARS-CoV-2-positive donors. Am J Transplant 2020;20:1795–9.
16 Sanghavi DK, Lowman PE, Harnois DM, et al. Changes in liver transplant center practice in response to coronavirus 2019: Unmasking dramatic center-level variability. Liver Transpl 2020;26:1672–3.
17 Martini S, Patrono D, Pittaluga F, et al. Urgent liver transplantation soon after recovery from COVID-19 in a patient with decompensated liver cirrhosis. Hepatol Commun 2020;5:144–5.
18 Goss MB, Munoz FM, Ruan W, et al. Liver transplant in a recently COVID-19 positive child with hepatoblastoma. Pediatr Transplant 2020: e13880.
19 Rouphael C, D'Amico G, Ricci K, et al. Successful orthotopic liver transplantation in a patient with a positive SARS-CoV2 test and acute liver failure secondary to acetaminophen overdose. Am J Transplant 2020 Oct 5;[E-pub ahead of print].
20 Strauss AT, Boyarsky BJ, Garonzik-Wang JM, et al. Liver transplantation in the United States during the COVID-19 pandemic: National and center-level responses. Am J Transplant 2020 Oct 27;[E-pub ahead of print].
21 Lisman T, Violi F. Cirrhosis as a risk factor for venous thrombosis. Thromb Haemost 2017;117:3–5.
22 De Pietri L, Montalti R, Nicolini D, et al. Perioperative thromboprophylaxis in liver transplant patients. World J Gastroenterol 2018;24:2931–48.
23 Jones K, Pham C, Aguilar C, et al. Retrospective review on the safety and efficacy of direct oral anticoagulants compared with warfarin in patients with cirrhosis. Fed Prac 2020;37:479–85.
24 Tripodi A, Primignani M, Mannucci PM, et al. Changing concepts of cirrhotic coagulopathy. Am J Gastroenterol 2017;112:274–81.
25 Ballestri S, Capitelli M, Fontana MC, et al. Direct oral anticoagulants in patients with liver disease in the era of non-alcoholic fatty liver disease global epidemic: A narrative review. Adv Ther 2020;37:1910–32.
26 Weinberg EM, Palecki J, Reddy KR. Direct-acting oral anticoagulants (DOACs) in cirrhosis and cirrhosis-associated portal vein thrombosis. Semi Liver Dis 2019;39:195–208.
27 Ambrosino P, Tarantino L, Di Minno G, et al. The risk of venous thromboembolism in patients with cirrhosis. A systematic review and meta-analysis. Thromb Haemost 2017;117:139–48.
28 Lee SR, Lee HJ, Choi EK, et al. Direct oral anticoagulants in patients with atrial fibrillation and liver disease. J Am Coll Cardiol 2019;73:3295–308.
29 Lapumnuaypol K, DiMaria C, Chiasakul T. Safety of direct oral anticoagulants in patients with cirrhosis: A systematic review and meta-analysis. QJM 2019;112:605–10.
30 Priyanka P, Kupec JT, Krafft M, et al. Newer oral anticoagulants in the treatment of acute portal vein thrombosis in patients with and without cirrhosis. Int J Hepatol 2018:8432781.
31 Loffredo L, Pastori D, Farcomeni A, et al. Effects of anticoagulants in patients with cirrhosis and portal vein thrombosis: A systematic review and meta-analysis. Gastroenterology 2017;153:480–7.
32 Davis KA, Joseph J, Nisly SA. Direct oral anticoagulants and warfarin in patients with cirrhosis: A comparison of outcomes. J Thromb Thrombolysis 2020;50:457–61.
33 Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. N Engl J Med 2011;365:147–56.
34 Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest 2016;149:315–52.
35 Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. Chest 2018;154:1121–201.
36 Mort JF, Davis JPE, Mahoro G, et al. Rates of bleeding and discontinuation of direct oral anticoagulants in patients with decompensated cirrhosis. Clin Gastroenterol Hepatol 2020 Aug 8;[E-pub ahead of print].
37 Elhosseiny S, Moussawi HA, Chalhoub JM, et al. Direct oral anticoagulants in cirrhotic patients: Current evidence and clinical observations. Can J Gastroenterol Hepatol 2019 Jan 8;[E-pub ahead of print].
38 Caldeira D, Barra M, Santos AT, et al. Risk of drug-induced liver injury with the new oral anticoagulants: Systematic review and meta-analysis. Heart 2014;100:550–6.
39 Alonso A, MacLehose RF, Chen LY, et al. Prospective study of oral anticoagulants and risk of liver injury in patients with atrial fibrillation. Heart 2017;103:834–9.
40 Kato ET, Giugliano RP, Ruff CT, et al. Efficacy and safety of edoxaban in elderly patients with atrial fibrillation in the ENGAGE AF-TIMI 48 trial. J Am Heart Assoc 2016;5:e003432.
41 Qamar A, Antman EM, Ruff CT, et al. Edoxaban versus warfarin in patients with atrial fibrillation and history of liver disease. J Am Coll Cardiol 2019;74:179–89.
42 Intagliata NM, Maitland H, Caldwell SH. Direct oral anticoagulants in cirrhosis. Curr Treat Options Gastroenterol 2016;14:247–56.
43 Intagliata NM, Henry ZH, Maitland H, et al. Direct oral anticoagulants in cirrhosis patients pose similar risks of bleeding when compared to traditional anticoagulation. Dig Dis Sci 2016;61:1721–7.
44 Hum J, Shatzel JJ, Jou JH, et al. The efficacy and safety of direct oral anticoagulants vs traditional anticoagulants in cirrhosis. Eur J Haematol 2017;98:393–7.
45 Lee HJ, Choi EK, Rhee TM, et al. Cirrhosis is a risk factor for atrial fibrillation: A nationwide, population-based study. Liver Int 2017;37:1660–7.

46 Hoolwerf EW, Kraaijpoel N, Buller HR, et al. Direct oral anticoagulants in patients with liver cirrhosis: A systematic review. Thromb Res 2018;170:102–8.
47 Mannucci PM, Tripodi A. Direct oral anticoagulants and cirrhosis: More evidence still needed for efficacy and safety in portal vein thrombosis. Vasc Pharm 2019;113:92–3.
48 Sanches-Ocana R, Tejedor-Tejada J, Cimavilla-Roman M, et al. Utility of oral anticoagulants as prophylaxis of recurrent portal thrombosis after liver transplantation. Transplant Proc 2019;51:83–6.
49 Janczak DT, Mimier MK, McBane RD, et al. Rivaroxaban and apixaban for initial treatment of acute venous thromboembolism of atypical location. Mayo Clin Proc 2018;93:40–7.
50 Kamel Y, Hassanin A, Ahmed AR, et al. Perioperative thromboelastometry for adult living donor liver transplant recipients with a tendency to hypercoagulability: A prospective observational cohort study. Transfus Med Hemother 2018;45:404–12.
51 Mohan BP, Aravamudan VM, Khan SR, et al. Treatment response and bleeding events associated with anticoagulant therapy of portal vein thrombosis in cirrhotic patients: Systematic review and meta-analysis. Ann Gastroenterol 2020;33:521–7.
52 Feltracco P, Barbieri S, Cillo U, et al. Perioperative thrombotic complications in liver transplantation. World J Gastroenterol 2015;21:8004–13.
53 Santeusanio AD, Weinberg AD, Florman SS, et al. Safety of direct-acting oral anticoagulants relative to warfarin in a matched cohort of liver transplant recipients. Clin Transplant 2019;34:e13756.
54 Lichvar AB, Pierce DR, Salerno D, et al. Utilization of direct-acting oral anticoagulation in solid organ transplant patients: A national survey of institutional practices. Clin Transplant 2020;34:e13853.
55 Vuilleumier PH, Nagler M, Beldi G, et al. Orthotopic liver transplant in a patient anticoagulated with rivaroxaban: A case report. A Pract 2019;13:54–7.
56 Cuker A, Burnett A, Triller D, et al. Reversal of direct oral anticoagulants: Guidance from the anticoagulation forum. Am J Hematol 2019;94:697–709.
57 Feltracco P, Carollo C, Barbieri S, et al. Pain control after liver transplantation surgery. Transplant Proc 2014;46:2300–7.
58 Eisenach JC, Plevak DJ, Van Dyke RA, et al. Comparison of analgesic requirements after liver transplantation and cholecystectomy. Mayo Clin Proc 1989;64:356–9.
59 Moretti EW, Robertson KM, Tuttle-Newhall JE, et al. Orthotopic liver transplant patients require less postoperative morphine than do patients undergoing hepatic resection. J Clin Anesth 2002;14:4160420.
60 Tong K, Nolan W, O'Sullivan DM, et al. Implementation of a multimodal pain management order set reduces perioperative opioid use after liver transplantation. Pharmacotherapy 2019;39:975–82.
61 Chadha R, Pai S, Aniskevich S, et al. Nonopioid modalities for acute postoperative pain in abdominal transplant recipients. Transplantation 2020;104:694–9.
62 Kutzler HL, Gannon R, Nolan W, et al. Opioid avoidance in liver transplant recipients: Reduction in postoperative opioid use through a multidisciplinary multimodal approach. Liver Transpl 2020;26:1254–62.
63 Pai S, Aniskevich S, Rodrigues ES, et al. Analgesic considerations for liver transplantation patients. Curr Clin Pharmacol 2015;10:54–65.
64 Bergasa NV, Rothman RB, Mukerje E, et al. Up-regulation of central mu-opioid receptors in a model of hepatic encephalopathy: A potential mechanism for increased sensitivity to morphine in liver failure. Life Sci 2002;70:1701–8.
65 Jin SJ, Jung JY, Noh MH, et al. The population pharmacokinetics of fentanyl in patients undergoing living-donor liver transplantation. Clin Pharmacol Ther 2011;90:423–31.
66 Raucoules-Aime M, Kaidomar M, Levron J, et al. Hepatic disposition of alfentanil and sufentanil in patients undergoing orthotopic liver transplantation. Anesth Analg 1997;84:1019–24.
67 Lange H, Stephan H, Zielmann S, et al. Hepatic disposition of sufentanil in patients undergoing coronary bypass surgery. Acta Anaesthesiol Scand 1993;37:154–8.
68 Bailey PL, Streisand JB, East KA, et al. Differences in magnitude and duration of opioid-induced respiratory depression and analgesia with fentanyl and sufentanil. Anesth Analg 1990;70:8–15.
69 Madan A, Barth KS, Balliet WE, et al. Chronic pain among liver transplant candidates. Prog Transplant 2012;22:379–84.
70 Vu JV, Cron DC, Lee JS, et al. Classifying preoperative opioid use for surgical care. Ann Surg 2020;271:1080–6.
71 DiMartini A, Crone C, Dew MA. Alcohol substance use in liver transplant patients. Clin Liver Dis 2011;15:727–51.
72 Randall HB, Alhamad T, Schnitzler MA, et al. Survival implications of opioid use before and after liver transplantation. Liver Transpl 2017;23:305–14.
73 Fukazawa K, Rodriguez PJ, Fong CT, et al. Perioperative opioid use and chronic post-surgical pain after liver transplantation: A single center observational study. J Cardiothorac Vasc Anesth 2020;34:1815–21.
74 Markin NW, Kassel CA, Chacon MC. Preoperative narcotic weaning in the perioperative patient: Now is the time. J Cardiothorac Vasc Anesth 2020;34:1822–3.
75 Kwon S, Thompson R, Dellinger P, et al. Importance of perioperative glycemic control in general surgery. Ann Surg 2013;257:8–14.
76 Kotagal M, Symons RG, Hirsch IB, et al. Perioperative hyperglycemia and risk of adverse events among patients with and without diabetes. Ann Surg 2015;261:97–103.
77 Duggan EW, Klopman MA, Berry AJ, et al. The Emory University perioperative algorithm in the management of hyperglycemia and diabetes in non-cardiac surgery patients. Curr Diab Rep 2016;16:34.
78 Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345:1359–67.
79 Ammori JB, Sigakis M, Englesbe MJ, et al. Effect of intraoperative hyperglycemia during liver transplantation. J Surg Res 2007;140:227–33.
80 Wallia A, Parikh ND, Molitch ME, et al. Post-transplant hyperglycemia is associated with increased risk of liver allograft rejection. Transplantation 2010;89:222–6.
81 Kumar SS, Pelletier SJ, Thompson A, et al. Intraoperative glycemic control in patients undergoing orthotopic liver transplant: A single center prospective randomized study. BMC Anesthesiol 2020;20:3.
82 Yoo S, Lee H, Lee H, et al. Association between perioperative hyperglycemia or glucose variability and postoperative acute kidney injury after liver transplantation: A retrospective observational study. Anesth Analg 2017;124:35–41.
83 Galindo RJ, Wallia A. Hyperglycemia and diabetes mellitus following organ transplantation. Curr Diab Rep 2016;16:14.
84 Lieber SR, Lee R, Jiang Y, et al. The impact of post-transplant diabetes mellitus on liver transplant outcomes. Clin Transplant 2019;33:e13554.
85 Moon JI, Barbeito R, Faradji RN, et al. Negative impact of new-onset diabetes mellitus on patient and graft survival after liver transplantation: Long-term follow up. Transplantation 2006;82:1625–8.
86 Roccaro GA, Goldberg DS, Hwang WT, et al. Sustained posttransplantation diabetes is associated with long-term major cardiovascular events following liver transplantation. Am J Transplant 2018;18:207–15.
87 Gitto S, De Maria N, Marzi L, et al. Pre-transplant diabetes predicts atherosclerotic vascular events and cardiovascular mortality in liver transplant recipients: A long-term follow-up study. Eur J Intern Med 2020;79:70–5.
88 Zelada H, VanWagbner LB, Pollack T, et al. Development of a predictive model for hyperglycemia in nondiabetic recipients after liver transplantation. Transplant Direct 2018;4:e393.
89 Fatourou EM, Tsochatzis EA. Management of metabolic syndrome and cardiovascular risk after liver transplantation. Lancet Gastroenterol Hepatol 2019;4:731–41.