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REVIEW ARTICLE

CAQ Corner

CAQ Corner: Surgical evaluation for liver transplantation

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Abstract
The evaluation of a liver transplantation candidate is a complex and detailed process that in many cases must be done in an expedited manner because of the critically ill status of some patients with end-stage liver disease. It involves great effort from and the collaboration of multiple disciplines, and during the evaluation several studies and interventions are performed to assess and potentially prepare a patient for liver transplant. Here we review the liver transplantation evaluation from a surgical perspective.

INTRODUCTION

Liver transplantation is a complex multidisciplinary field requiring the collaboration of many different health care providers. The decision to list and transplant patients with end-stage liver disease is done with the consensus of the entire transplant team, including the patient, hepatologists, transplant surgeons, anesthesiologists, social workers, psychologists, and transplant coordinators. From a surgical perspective, one must determine whether a patient with end-stage liver disease will tolerate a liver transplant and if it is technically feasible, prior to proceeding to the operating room (OR). When determining transplant candidacy in patients with high Model for End-Stage Liver Disease scores who are critically ill, there is a delicate balance between optimizing a patient for liver transplantation and proceeding to the OR if an appropriate organ offer is available. Here we review some of the salient aspects of the surgical evaluation for liver transplantation, specifically perioperative and technical considerations.

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MEDICAL PERIOPERATIVE CONSIDERATIONS

In addition to the overall assessment of transplant candidacy, the transplant surgeon must identify any risk factors for perioperative morbidity or mortality

Abbreviations: CAD, coronary artery disease; CRRT, continuous renal replacement therapy; CT, computed tomography; DCD, donation after circulatory death; EAD, early allograft dysfunction; ERCP, endoscopic retrograde cholangiopancreatography; HAT, hepatic artery thrombosis; HD, hemodialysis; HE, hepatic encephalopathy; HPB, hepatopancreaticobiliary; IVC, inferior vena cava; LRV, left renal vein; OR, operating room; pHTN, pulmonary hypertension; PTBD, percutaneous transhepatic biliary drainage; PV, portal vein; PVT, portal vein thrombosis; RV, right ventricle; SMV, superior mesenteric vein; SV, splenic vein; TIPS, transjugular intrahepatic portosystemic shunt; UW, University of Wisconsin.

and technical barriers to completing a liver transplant. Specific aspects of a patient's medical history that would be relevant to perioperative risk include advanced age, any history of coronary artery disease (CAD), heart failure, pulmonary hypertension (pHTN), hepatopulmonary syndrome, cerebrovascular disease, chronic kidney disease or end-stage renal disease, or longstanding diabetes mellitus.[1–3] Preoperative cardiopulmonary assessment with echocardiography, stress test, and/or potential cardiac catheterization, left for CAD and right for pulmonary artery pressures, is critical. The degree of pHTN may be evaluated by echocardiography or a Swan-Ganz catheter. In patients with pHTN, it is important to identify the etiology, primary versus secondary to hepatopulmonary syndrome or volume overload. Etiology will dictate further optimization by, for example, pulmonary vasodilators, diuresis, or dialysis.

Many of these comorbidities have the potential to impact a patient's volume status, which undergoes massive shifts during the liver transplant operation.[4] Although underlying cardiopulmonary pathophysiology can result in marked intraoperative morbidity and even mortality, the volume shifts and the hemodynamic variation associated with the transplant procedure itself can exacerbate these underlying conditions, even if mild, leading to significant morbidity and mortality as a result of myocardial infarction, refractory hypoxemia, stroke, or cardiac arrest in the perioperative period.[5] It is hence especially critical to perform a detailed cardiopulmonary assessment and evaluate if there are potential preoperative interventions to minimize the risk of cardiovascular events.

Even in the patient with relatively few of these comorbidities, an assessment of the patient's current clinical status is also critical to determine if it is suitable to tolerate a liver transplant.[6,7] An uncontrolled active infection, for example, is an absolute contraindication to transplantation. For patients admitted to the intensive care unit, the amount of pressors, presence of renal failure on hemodialysis (HD) or continuous renal replacement therapy (CRRT), and respiratory status all must be considered. High pressor requirements, high pulmonary arterial pressures, and volume overload are all relative contraindications to liver transplantation. Multiple high-dose pressors and mean pulmonary artery pressure greater than 35 mm Hg are often used as prohibitive contraindications to transplant. Neurologic status must also be assessed, especially in cases of severe hepatic encephalopathy (HE) necessitating intubation—an evaluation of the reversibility of a worsening neurologic condition is essential before proceeding with transplantation. Assessment with serial computed tomography (CT) head scans or placement of an external ventricular drain may be required.

The ability to improve the patient's clinical status, for example, by removing volume via diuresis or dialysis, and estimation of their physiologic reserve in addition to discussions with colleagues from anesthesia help determine whether it is feasible to get the patient through a liver transplantation at the time that an organ offer is available. Table 1 lists some absolute and relative contraindications to liver transplantation, but it is important to note that these contraindications can vary somewhat from center to center depending on the resources or ability to manage particular preoperative risks, such as severe pHTN.

A patient's frailty, which can be related to his or her current clinical status, has emerged as an important predictor of mortality in patients on the waiting list for liver transplantation and has thus become a factor in decision making for proceeding with liver transplantation.[8,9] Measures of frailty, including the Fried Frailty Score, Short Physical Performance Battery, and Instrumental Activities of Daily Living Scale, have been shown to correlate with waitlist mortality.[9] These scoring systems capture varying attributes that may affect frailty, which may depend on factors including functional status, exercise tolerance, and physiologic reserve. Measures and definitions of frailty specific to patients with cirrhosis are being developed, which may be more widely adopted and employed in the future.[10,11] Patients who are prohibitively frail often require nutritional optimization, such as supplemental enteral feeds, and aggressive physical and occupational therapy.

If a patient is an appropriate candidate for liver transplantation, a donor organ offer must be evaluated and determine if it is a suitable for the recipient. Characteristics of the donor liver that are assessed include donor history of alcohol use or other risk factors for liver disease, the trend of liver enzymes, and fat content as assessed by imaging or biopsy at the time of procurement. The donor liver must be an appropriate size for the recipient. The size of the liver is estimated based on donor weight and height and measurements

TABLE 1 Absolute and relative contraindications for liver transplantation

Absolute contraindications	Relative contraindications
Uncontrolled infection	Pressor requirement
Untreated obstructive CAD	pHTN
	Volume overload
	Cardiac valvular disease
	Morbid obesity
	Prior stroke with residual deficits
	PVT
	Complicated anatomy including prior surgery

Abbreviations: CAD, coronary artery disease; pHTN, pulmonary hypertension; PVT, portal vein thrombosis.

from cross-sectional imaging if available. Other factors, including anticipated cold ischemia time and/or the use of extended criteria liver offers (which includes donors with prolonged cold ischemia time, advance age, a high level of macrosteatosis, a high body mass index, and elevated terminal transaminases or bilirubin and donations after circulatory death [DCDs]), may increase the risk of early allograft dysfunction (EAD). Anticipating if a potential recipient can tolerate EAD factors into donor and recipient matching.[12] The use of extended criteria donors can also be associated with more severe reperfusion syndrome, and therefore these grafts must be carefully considered in recipients with marginal cardiopulmonary status.

TECHNICAL CONSIDERATIONS

From a technical perspective, a careful review of the patient's vascular anatomy (hepatic arterial, portal venous, hepatic veins), liver morphology, degree of portal hypertension, body habitus, and impact and extent of prior surgery on cross-sectional imaging is imperative to determining the feasibility of transplantation. Relevant prior abdominal surgical history includes upper abdominal surgery, including gastric surgery, cholecystectomy, hepatic resections, and pancreatic resections. The Kasai procedure for biliary atresia and prior liver transplantation are other special considerations. An abdomen with dense adhesions from multiple prior surgeries is also challenging as adhesiolysis can be time consuming and contribute to high blood loss. Prior surgeries are not absolute contraindications to transplantation but must be considered in conjunction with the history and clinical status of the transplant candidate.

The presence of a transjugular intrahepatic portosystemic shunt (TIPS), location of varices or shunts if present, and presence of portal vein thrombosis (PVT) are additional factors driving the technical feasibility of a liver transplant. A four-phase liver protocol CT scan is one of the best tools available to assess these factors, which can also be used to assess for hepatocellular carcinoma. PVT is not an absolute contraindication to transplantation, but it increases the technical difficulty and likely the length of the operation, which can be important, especially when considering candidates who are critically ill. The chronicity and extent of PVT can influence what may be done intraoperatively, which will be discussed later. The arterial system is assessed for disease (atherosclerosis) and for aberrant anatomy, such as a replaced right or left hepatic artery, which may necessitate placement of an aortic interposition graft. If present, the location of a TIPS can affect surgical planning as well. Ideally, the TIPS is positioned so that it does not extend in the portal vein (PV), remaining in the right PV, or the inferior vena cava (IVC), remaining in the right hepatic vein, assuming a conventionally placed right-sided TIPS. If it does extend into either the PV or vena cava, the choice of clamp or approach to vascular control of these structures may need to be adjusted during the hepatectomy and ultimately for liver transplantation to be feasible. An algorithm shown in Figure 1 summarizes some of the most salient aspects of the approach to liver transplantation evaluation from a surgical perspective.

Portal vein thrombosis

The extent and chronicity of PVT factors into the feasibility and surgical planning for liver transplantation. In

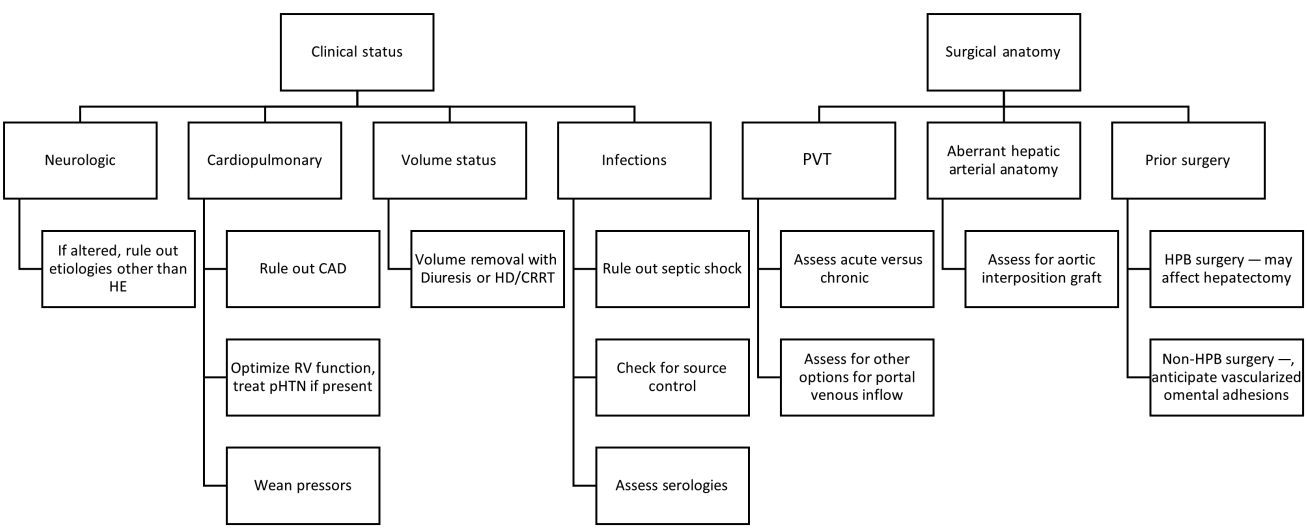

FIGURE 1 Framework for the assessment of operative readiness for liver transplantation from a surgical perspective.

the absence of PVT, or a prohibitively diminutive portal vein, the donor PV is anastomosed to the recipient PV in a tension-free fashion that also avoids redundancy. If the PVT is partially occlusive and chronic, there may nonetheless be adequate flow such that a PV-to-PV anastomosis is sufficient—the adequacy of flow can be assessed intraoperatively with Doppler ultrasound to measure flows. A partial thrombectomy can be attempted but is less likely to be successful with chronic PVT, depending on the intraoperative assessment of flow and how adherent the clot is to the vessel wall.[13] An occlusive PVT not amenable to thrombectomy generally necessitates a different source of splanchnic inflow for the liver allograft. However, in the setting of an acute PVT, thrombectomy may be possible, although it is important to assess whether the patient has signs of bowel ischemia as an interventional radiology-guided thrombectomy may be required prior to transplantation. Also, these patients will often require some form of anticoagulation, which can increase the risk of gastrointestinal bleeding events in patients with advanced liver disease and portal hypertension.

In cases where it is not feasible to use the recipient PV as inflow to the donor PV, an alternative route is required. Often, the next option involves the use of a graft or conduit, generally via a cadaveric iliac vein, from the recipient superior mesenteric vein (SMV) to the donor PV, as shown in Figure 2, if the SMV has an adequate landing zone (free of thrombus) to allow for vascular control and anastomosis.[14] If an adequate site is not available on the SMV, other sources of inflow such as large varices or shunts, such as an enlarged coronary vein, may be explored as options.[15] The feasibility of a shunt or large varix depends on its location, ability to be isolated for enough distance for clamping, and length of the available graft, which is again generally a cadaveric iliac vein. In the case of an adequately sized (i.e., adequate flow) splenorenal shunt, the left renal vein (LRV) can also be used.[16] Complete and/or diffuse mesenteric and portal venous thrombosis is considered a contraindication to liver transplantation, and these patients are often referred for multivisceral (liver, small bowel, etc.) transplantation.[17]

Complications from the portal anastomosis include PV stenosis or recurrent thrombosis, which can be categorized as acute or chronic. PV stenosis or recurrent PVT is not always clinically relevant, as the portal flow may be adequate as evaluated by Doppler ultrasound. It can present clinically with vague signs and symptoms, such as unexplained altered mental status or recurrent ascites, and especially in the acute setting can manifest more prominently with overt graft failure. In the chronic setting, PVT may not be clinically relevant especially if collateral flow to the liver allograft has developed or can present clinically with signs and symptoms of portal hypertension. Clinically relevant PV stenosis can sometimes be a diagnosis of exclusion after ruling out other etiologies of graft failure such as rejection. Ultimately, after revision, either operatively or by interventional radiology with venoplasty with or without a stent, the diagnosis is apparent with a resolution of symptoms and/or graft failure after intervention. Outcomes with respect to PVT are heterogeneous. In

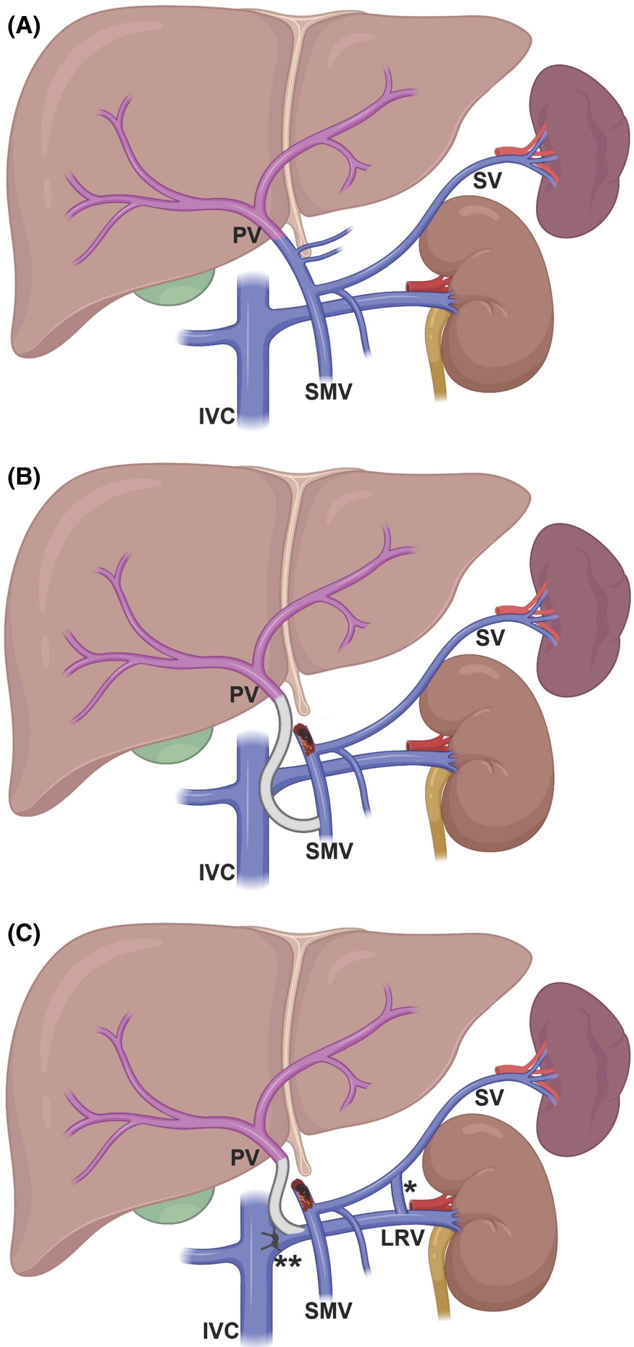

FIGURE 2 Surgical approaches to establishing inflow in the setting of PVT. (A) Standard donor PV to recipient PV anastomosis. (B) SMV interposition graft, generally performed using a donor iliac vein conduit, in the setting of PVT. (C) Renoportal interposition graft in the setting of PVT and splenorenal shunt (*). Note that the LRV is ligated on the caval side (**). Not drawn to scale. Created with BioRender.com.

one meta-analysis that reviewed 23,932 liver transplantations, the incidence of PVT was 7.3%, and the presence of a PVT was associated with increased mortality in earlier studies, whereas more recent studies have shown no difference between patients with and without PVT.[18]

Portosystemic shunts

As discussed previously in the case of PVT, large portosystemic shunts may be used as inflow to the donor PV. Otherwise, in the setting of a standard PV-to-PV anastomosis, there are recent data promoting intraoperative ligation to prevent a “steal” with the diversion of portal venous flow away from the liver.[19] Determining the hemodynamic importance of a shunt can be assessed by its diameter and length to assess resistance, and intraoperative Doppler ultrasound can be performed to measure flows.

In the absence of portosystemic shunts, attention should be paid in the timing of PV clamping before completion of hepatectomy as the bowel can consequently become markedly edematous and can also prompt acute gastrointestinal bleeding. Surgical construction of a shunt can be employed to alleviate such complications. In cases where the hepatectomy is challenging and/or in the absence of portosystemic shunts, a temporary portocaval shunt or the use of venovenous bypass can be considered, which alleviates the acute portal hypertension and can thus avoid these sequalae. In the case of a portocaval shunt, the PV is anastomosed directly to the IVC. Venovenous bypass involves redirecting the portal and venous flow to an extracorporeal pump that returns the blood to the superior vena cava via a large catheter in the axillary or internal jugular vein.

Caval anastomosis and outflow considerations

There are several options for reconstructing the outflow of the donor liver to the cava. A common technique is the “piggyback” method, which requires that during hepatectomy the subhepatic vena cava is preserved and in turn necessitates ligation of all short hepatic veins.[20] The donor cava is anastomosed to the orifices of the recipient hepatic veins that were divided. Another option is a side-to-side cavocavostomy where the donor cava is anastomosed longitudinally to the recipient cava.[20,21] This may be used, for example, when the hepatic veins are small or if the right hepatic vein is large and vertically oriented. The piggyback technique is not always feasible if the dissection of the liver away from the IVC is impeded by, for example, bleeding or a caudate that completely encapsulates the IVC. In these cases, the more “traditional” bicaval approach, where the retrohepatic cava is also resected en bloc with the liver during hepatectomy, and two venous anastomoses to the cava are performed, with one anastomosis to the suprahepatic cava and the other to the infrahepatic cava.[21]

Ensuring adequate outflow is particularly important in the case of partial liver transplantation, that is, split livers or living donor livers. Often the middle hepatic vein needs to be reconstructed to provide sufficient outflow—the reconstruction can include using an interposition vein graft or direct anastomosis to the cava depending on its relative location. Inadequate outflow can manifest as relative portal hypertension and/or graft failure and can contribute to the “small-for-size” syndrome.[22]

Reperfusion

After the caval and portal anastomoses are complete, the liver is reperfused with unclamping of the corresponding vessels. The sudden increase in venous return to the right ventricle can cause a variety of hemodynamic consequences. The venous return includes residual preservation solution, commonly containing high potassium, and mesenteric blood that has been relatively stagnant, potentially accumulating various proinflammatory molecules. All of these factors can contribute to what is known as “reperfusion syndrome,” which may have varying degrees of severity depending on the components of the venous return. The reperfusion syndrome includes increases in central venous pressure and pulmonary arterial pressures and decreases in mean arterial pressure and peripheral vascular resistance.[23,24]

To limit the effects of reperfusion, several measures are taken intraoperatively. Before reperfusion, the liver allograft is flushed with cold crystalloid solution low in potassium to reduce the potassium load if the University of Wisconsin (UW) preservation solution has been used (that has a high potassium concentration), which can be done on the back table or before the caval anastomosis is complete. As opposed to a crystalloid flush, some centers employ a blood flush or both; in our center, a crystalloid flush is typically performed when UW has been used for organ preservation, although a blood flush is also performed especially when the warm ischemia time is prolonged. It is thought that the cold ischemia time can also affect the severity of reperfusion syndrome, and therefore minimizing this time is ideal. Finally, continuous assessment of right ventricle function and pulmonary arterial pressures is critical through the use of Swan-Ganz catheters and transesophageal echocardiography probes, for example. Poor cardiac function and pHTN can exacerbate the effects of reperfusion (and during clamping of IVC to allow for sewing the anastomosis), even leading to intraoperative cardiac arrest.[23]

Aberrant hepatic arterial anatomy

One of the most dreaded posttransplant complications is acute hepatic artery thrombosis (HAT), which can lead to primary nonfunction and prompt emergent retransplant. Thus, careful consideration of the quality of donor and recipient vessels, size match, and orientation must be taken into account during the transplant procedure. Similar to the other anastomoses, an ideal arterial anastomosis is tension free but has limited redundancy. The hepatic artery lumen can be quite small; therefore, the anastomosis is often made between branch points in the arteries as they have relatively more arterial wall to lumen size, which prevents the artery from narrowing at the anastomosis from the sutures. It is not uncommon to encounter variant arterial anatomy. Some retrospective studies of CT angiograms performed on patients for various reasons suggest that conventional hepatic arterial anatomy may be found in as low as 50%–55% of cases.[25,26] The two most common variants found are a replaced hepatic right artery, which comes off the superior mesenteric artery and courses laterally in the porta hepatis and is posterior to the common bile duct, and a replaced left artery, which comes off the left gastric artery and courses through the gastrohepatic ligament. In these cases, either the replaced artery or proper artery may be used depending on the lumen size match of donor to recipient. If none of the arteries available are of adequate size, an aortic conduit, often using a cadaveric iliac artery, may be used to provide inflow to the donor artery directly from the aorta. Depending on the anatomy of the patient and his or her surgical history, a supraceliac or infrarenal aortic conduit may be constructed. Evaluation of hepatic arterial flow is done with an intraoperative Doppler assessment. Sometimes low arterial flow can result from abnormally high portal flows, a homeostatic mechanism referred to as the hepatic artery buffer response. In these cases, ligation of the splenic artery or even a splenectomy can be considered for flow modulation.

Clinical manifestations from arterial complications occur across a spectrum from acute HAT to chronic stenosis or kinking. These may not manifest with severe aberrations in liver biochemistries. Therefore, an evaluation of the hepatic vasculature by Doppler ultrasound is a useful tool, especially in the early postoperative period, to evaluate the arterial anastomosis.[27] If an arterial stenosis or thrombosis is identified, surgical revision or interventional radiology-guided angioplasty with or without a stent is generally performed.

Biliary considerations

The main principles of anastomosis hold for the biliary anastomosis, in particular avoiding tension and redundancy. The blood flow to the bile duct is essential, the arteries supplying it lie at the three and nine o'clock positions, and care must be taken to avoid injuring these too distal to the anastomosis. In addition, limiting the length of donor bile duct is important as shorter length can limit relative ischemia. The size of the donor and recipient ducts ideally should be similar. If there is a large size discrepancy for which the recipient or donor duct cannot be modified appropriately for a duct-to-duct anastomosis, a Roux-en-Y hepaticojejunostomy is performed.[28] Intraoperatively, a stent can be placed depending on the individual surgeon's preference, but it has not been shown to decrease the rate of biliary complications.[29]

Biliary complications include leaks and strictures, which are not uncommon. The rates of biliary complications are notably higher in DCD and living donor recipients. Compared with a rate of approximately 15% for deceased donors after brain death, the rate of biliary complications in DCD and living donor recipients can be as high as 20% and 30%, respectively.[30,31] Biliary leaks can potentially be managed by endoscopic retrograde cholangiopancreatography (ERCP), percutaneous intraabdominal drainage, or percutaneous transhepatic biliary drainage (PTBD), and they generally are identified early postoperatively and addressed operatively especially if they are large leaks, which tend to have marked clinical effects.[32,33] Biliary leaks can also predispose a bile anastomosis to subsequent stricture.

In general, the etiology of a biliary stricture is technical, ischemic, or some combination of both. Direct blood flow to the anastomosis may be compromised if the arteries supplying the bile ducts are ligated too proximal or too distal to the anastomosis. Ischemia to the bile duct can also be secondary to inadequate hepatic arterial supply, which can result in nonanastomotic biliary stricture or even a more diffuse ischemic cholangiopathy that affects both intra- and extrahepatic ducts.[30] The mainstay of the postoperative management of biliary strictures is ERCP.[32] Although magnetic resonance cholangiopancreatography is often performed for diagnosis, ERCP can be both diagnostic and therapeutic, and in general a stent is placed across the biliary anastomosis. In cases where the biliary system cannot be decompressed adequately by ERCP, which can be the case with intrahepatic strictures, PTBD can be used.[33]

CONCLUSIONS

In summary, key factors involved in the surgical decision making regarding liver transplantation include a thorough assessment of a patient's cardiopulmonary history; current clinical status including cardiac, respiratory, and volume status; and hepatic anatomy, including the presence of PVT or TIPS. The criteria for several of these factors are difficult to evaluate in randomized control trials and can vary from center to center and depend on experience. At the same time, more studies are being published suggesting the importance of other factors, such as frailty, and the potential to transplant more patients with the use of machine perfusion or xenotransplantation. Each of these topics warrant an in-depth analysis of their own. With these advances, the tenets of the surgical evaluation will likely remain similar, but we expect that liver transplantation candidacy may continue to change and become more inclusive as advances in perioperative management and technique continue.

KEY POINTS

- Cardiopulmonary assessment and optimization are critical for potential transplant candidates.
- Frailty assessment has emerged as a potential critical predictor of transplant outcomes.
- PVT is not an absolute contraindication to transplantation but increases the technical complexity of the operation.
- Reperfusion is a critical step of liver transplantation and can be greatly affected by preoperative cardiopulmonary and volume status.
- The rate of biliary complications is higher in DCD and living donor recipients.

QUESTIONS

1. From a surgical perspective, what is an absolute contraindication to liver transplantation?
   a. history of Kasai procedure
   b. uncontrolled infection
   c. vasopressin requirement on renal replacement therapy
   d. portopulmonary hypertension
2. Which step of liver transplantation can be greatly affected by use of an extended criteria donor allograft?
   a. hepatectomy
   b. portal vein (PV) anastomosis
   c. arterial anastomosis
   d. reperfusion
3. In a patient with an acute PVT, what diagnosis should be urgently ruled out and managed prior to considering transplantation?
   a. renal failure
   b. hepatic encephalopathy (HE)
   c. bowel ischemia
   d. acute liver failure
4. Which types of donors place transplant recipients at increased risk for postoperative biliary complications?
   a. donation after circulatory (DCD) donors
   b. DBD donors
   c. living donors
   d. a and b
5. What is the most common etiology of ischemic cholangiopathy?
   a. inadequate hepatic arterial flow
   b. early bile duct stricture
   c. primary sclerosing cholangitis (PSC)
   d. portosystemic shunt

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CONFLICT OF INTEREST

Nothing to report.

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