Review Article

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Liver Transplantation: Contraindication and Ineligibility

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Liver transplantation (LT) is a life-saving therapeutic modality for patients with various advanced liver diseases. It is crucial to identify that the patient's illness is sufficiently advanced and unlikely to improve with medical management to justify the need for transplantation. At the same time, it is crucial to identify patients with co-morbidities and far advanced disease that would result in an unacceptable outcome after LT. Specific care also is required before deciding on LT in the elderly, acute on chronic liver disease, patients with comorbidities, and hepatocellular carcinoma. Transplantation needs to be timed appropriately to avoid unnecessary LT and ensure that the decision is not left too late to avoid losing the patient without a transplant. Also, important is the decision as to when not to transplant. The current review explores some of these issues of contraindications and ineligibility for LT. (J Clin Exp Hepatol xxxx;xxx:xxx)

The basic principles in selecting patients for liver transplantation (LT) are that the patient should have irreversible liver disease that will be fatal without LT, the patient should be fit enough to survive the surgery and post-operative period, and the patient should have a better quality of life and survival with transplantation than without transplantation. The patient should not be considered for LT if the liver disease is not advanced, the recipient has significant comorbidities which will decrease the success of LT, the donor or the graft is inappropriate, or LT is precluded by logistic reasons. In the context of liver transplantation, contraindication, futility, and ineligibility are closely overlapping terms. Contraindications to LT are generally agreed situations where transplant teams would not consider the patient for transplantation despite the patient having advanced liver disease. In most such cases, a transplant would be futile as the transplant is either not likely to be successful or result in poor quality of life despite a functioning graft e.g. patients with advanced cardiopulmonary disease or a patient of acute liver failure (ALF) with brain herniation.

Severe cardiopulmonary disease, uncontrolled sepsis, extrahepatic malignancy, uncontrolled hepatocellular carcinoma (HCC), and illicit drug use are absolute contraindications. HCC without vascular involvement or extrahepatic spread may be considered for transplantation after downstaging. Ongoing alcohol misuse has also been considered an absolute contraindication. The duration of abstinence should not be the only criterion for LT in alcoholic liver disease (ALD), and LT may be done in patients after a psychological assessment for commitment to alcohol abstinence and family support. Relative contraindications for LT include advanced age, obesity with body mass index (BMI) >35 kg/m^2, extensive abdominal surgeries, or extensive vascular thrombosis, which may be a challenge for the surgical procedure. The contraindications for LT are given in Table 1.

Keywords: liver transplantation, contraindications, ineligibility, chronic liver disease, acute liver failure

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Abbreviations: ACLF: acute on chronic liver failure; AIH: autoimmune hepatitis; AKI: acute kidney injury; ALD: alcoholic liver disease; ALF: acute liver failure; ALT: alanine aminotransferase; APASL: Asian Pacific Association for Study of the Liver; BCS: Budd–Chiari syndrome; BMI: body mass index; CAD: coronary artery disease; CAR–OLT: Cardiovascular Risk in Orthotopic Liver Transplantation; CHB: chronic hepatitis B; CKD: chronic kidney disease; CLD: chronic liver disease; CT: computerized tomography; CTP: Child–Turcotte–Pugh; DAA: directly acting antivirals; DDLT: deceased donor liver transplantation; EF: ejection fraction; ESLD: end-stage liver disease; GFR: glomerular filtration rate; GRWR: graft-to-recipient weight-ratio; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HE: hepatic encephalopathy; HIV: human immunodeficiency virus; HPS: hepatopulmonary syndrome; HRS: hepatorenal syndrome; INR: international normalized ratio; LRT: locoregional therapies; LT: liver transplantation; MELD: Model for End-stage Liver Disease; MPAP: mean pulmonary arterial pressure; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; NUCs: nucleoside analogs; PBC: primary biliary cholangitis; PCWP: pulmonary capillary wedge pressure; PoPH: portopulmonary hypertension; PSC: primary sclerosing cholangitis; PVR: pulmonary vascular resistance; RVSP: right ventricular systolic pressure; SBRT: stereotactic body radiotherapy; SKLT: simultaneous kidney and liver transplantation; TACE: transarterial chemoembolization; TARE: transarterial radioembolization

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Table 1 Contraindications to Liver Transplantation.

Absolute contraindications	Relative contraindications	Temporary contraindications
Severe cardiopulmonary disease	Extensive vascular thrombosis	Obesity (BMI >40 kg/m^2)
Hepatocellular carcinoma with vascular invasion, extrahepatic metastasis or beyond transplant criteria	Extensive abdominal surgeries	Positive cultures
Extrahepatic malignancy	Poor patient compliance	Untreated HIV
Active illicit drug use	Advanced age	Recent abstinence from alcohol
Ongoing alcohol abuse with lack of commitment to alcohol abstinence	Uncontrolled sepsis with multiorgan failure	Logistical constraints
Severe psychiatric illness		

Abbreviations: BMI, body mass index; HIV, human immunodeficiency virus.

Ineligibility is ascertained after the evaluation of patients referred for LT or after patients have undergone assessment for liver transplantation. Ineligible patients are refused for listing or taken off the transplant list. Ineligibility for LT after assessment is common and has been reported in as much as half the patients. Patients should be considered ineligible for a transplant if the disease process is reversible spontaneously or with medical management, if the patient requires medical optimization, or if the disease becomes too advanced for a successful outcome. As can be seen in Table 1, temporary contraindications are ineligibilities for transplant, which can be reversed after optimization. Some of the common reasons for ineligibility have been found to be inappropriate or premature referral for transplantation, medical comorbidities, and/or the need for medical optimization and the need for addiction rehabilitation.[1,2]

There are different challenges in the decision making for LT eligibility, not only in the broad groups of liver diseases [i.e., ALF, acute-on-chronic liver failure (ACLF), and chronic liver disease (CLD)] but also in specific etiologies like ALD, hepatitis B and C, autoimmune hepatitis (AIH), Budd–Chiari syndrome (BCS), etc. Moreover, there are special considerations in issues such as elderly patients, metabolic syndrome and obesity, cardiovascular comorbidities, renal dysfunction, hepatopulmonary syndrome (HPS), HCC, sarcopenia, and frailty. The current review aims to cover some of these issues which may make the patient ineligible for LT or the transplant may be contraindicated.

INELIGIBILITY FOR LT IN ACUTE LIVER FAILURE (ALF)

Despite improvements in the critical care for ALF, the transplant-free survival for ALF remains around 50%, and LT is an important therapeutic modality in ALF.[3] While the King's college criteria have been one of the most popular criteria for prognostication in ALF, they are plagued by poor sensitivity and they perform poorly in non-paracetamol etiologies.[4] Dynamic scores like the ALFED model appear attractive but require further validation.[5] While the initial scores of the patient may appear as that the patient does not require liver transplantation, they can rapidly deteriorate, and any patient of ALF with encephalopathy should be transferred to a liver transplant unit. Despite many criteria, the prognostic outcome and timing of LT remain difficult to predict. Transplanting too early may result in unnecessary LT as the patient may have survived without LT and would be subjected to lifelong unnecessary immunosuppression. On the other hand, waiting too long could result in patient becoming too sick for LT. Patient with ALF will become ineligible if they develop severe sepsis with positive blood cultures, significant hypotension despite high-dose ionotropic support, brain herniation, or brain death.

INELIGIBILITY FOR LT IN PATIENTS WITH CIRRHOSIS

The natural history of cirrhosis is characterized by an asymptomatic or compensated phase followed by a decompensated phase, which manifests with the complications of portal hypertension and liver dysfunction. Decompensation of cirrhosis in the form of variceal bleeding, ascites, jaundice, or encephalopathy occurs in 4–12% per year. The median survival varies depending on the type of decompensation. Patients with bleeding alone have better outcomes than patients with ascites without bleeding and much better outcomes than patients with bleeding and ascites. The five-year mortality risk with bleeding alone is 18%–20%, while in patients with non-bleeding manifestation like ascites, encephalopathy, or jaundice, the five-year mortality is in the range of 55–80%. The five-year mortality in patients who have two or more decompensations, like a combination of bleeding and ascites, may approach 88%.[6]

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The severity of liver disease had traditionally been assessed by the Child–Turcotte–Pugh (CTP) score, which considers the presence of ascites, HE, serum bilirubin, albumin, and an increase in prothrombin time more than the control. Each of these parameters is given 1–3 points based on the abnormalities, and patients are classified as Child A (5–6 points), B (7–9 points), or C (10–15 points). However, the CTP score is subjective with regard to the severity of encephalopathy and ascites. The Model for End-stage Liver Disease (MELD) score is more objective and is calculated based on the values of serum bilirubin, creatinine, and an international normalization ratio (INR).[7]

The optimal timing of LT is crucial to avoid intervening too early and give the patient a survival benefit. Merion *et al.*[8] evaluated the waiting list and post-transplant mortality in a cohort of 12,996 adults placed on the waiting list for LT. They showed that the survival benefit increased with the increasing MELD score. However, in patients with the MELD score <15, mortality was higher in transplanted patients than in those who did not receive a transplant.

The net survival benefit associated with MELD at LT has been calculated using generalized parametric models to quantify survival across MELD categories in 74196 adult liver transplants in the United States. A significant and progressively increasing survival benefit was seen in the MELD score of 18 or more. The expected additional life years after LT increased with increasing MELD: 0.2 years for MELD 11–15, 1.5 years for MELD 16–20, 3.5 years for MELD 21–25, 5.8 years for MELD 26–30, 6.9 years for MELD 31–34, and 7.2 years for MELD 35–40. However, the patients with MELD 6–10 were expected to lose life years after transplantation.[9]

Transplantation at low MELD scores is not associated with any demonstrable benefit. The MELD score of 15–17 represents a transition point beyond which a survival benefit is observed after LT. However, with sufficiently long follow-up, a subset of patients with lower MELD scores, except those less than 10, may also show a survival benefit.[10]

The minimal listing criteria proposed in 1997 were a CTP score of ≥7, which would identify patients with a one-year survival of 90% or less.[11] However, it was recognized that many patients meeting these criteria had low MELD scores. The American Association for the Study of Liver Diseases guidelines recommend that patients with cirrhosis should be referred for LT evaluation if CTP is ≥7, MELD is ≥10 or if the patient develops decompensation.[12] While these criteria may be appropriate to start evaluating the patients and keep them on close follow-up, it is generally accepted that LT should be considered in patients with cirrhosis who have decompensated cirrhosis or a MELD score ≥15.

MELDNa has been used as criteria for allocation in US since 2016. However, experts feel that the accuracy of prediction of mortality by MELD may have reduced.[13] Kim *et al.*[14] have proposed a revised version in form of MELD 3.0, which according to them affords more accurate mortality prediction in general than MELDNa and addresses determinants of waitlist outcomes including the sex disparity. However, more robust data are needed before it replaces MELDNa and becomes a standard for waitlist allocation.

While LT should not be considered in patients with a MELD score <15, patients with cirrhosis may, however, have significant encephalopathy, ascites, and gastrointestinal bleed despite having low MELD scores. In such cases, patients can be listed for LT despite low MELD if the patient has severe encephalopathy, uncontrolled ascites, or frequent GI bleeding. Also, there are certain patients who are sicker than their MELD score and MELD exception points are given to reduce waitlist mortality. Table 2 below mentions various conditions where MELD exception points are given.[15]

We also wish to highlight the importance of palliative care in advanced liver disease. There is a substantial population who are either not eligible or die waiting for a transplant. Palliative care is provided to patients and their families with a focus on the relief of symptoms by taking patient preferences into account. There is a need to adopt palliative services to help the terminally ill liver disease patient in living well during the final months or years. At the time of listing for LT, palliative care consultation should be

Table 2 Conditions With MELD Exception.

- MELD score <15 with complications of portal hypertension:
  - Chronic or recurrent encephalopathy
  - Recurrent gastrointestinal bleeding
  - Hepatic hydrothorax
  - Hepatopulmonary syndrome
  - Portopulmonary hypertension
- Related to malignant disease:
  - Perihilar cholangiocarcinoma*
  - Hepatic metastases of a gastrointestinal endocrine tumor
  - Rare liver tumors: Hepatic epithelioid hemangioendothelioma, hepatic angiosarcoma
- Complications of cholestatic disease:
  - Refractory pruritus
  - Recurrent bacterial cholangitis
- Miscellaneous
  - Polycystic liver disease
  - Familial amyloid polyneuropathy
  - HIV infection
  - Hereditary haemorrhagic telangiectasia

Abbreviations: HIV, human immunodeficiency virus; MELD, Model for End-stage Liver Disease.

*Malignant stricture on imaging (biopsy or cytology confirmed malignancy or aneuploidy or carbohydrate antigen 19-9 >100 U/mL in the absence of cholangitis); unresectable disease with a solitary tumor <3 cm in diameter without regional or distant metastasis and the patient should be administered neoadjuvant chemoradiation with staging laparotomy before LT.

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taken with a goal to characterize the patient's illness understanding, providing support for the high-risk decision, and improving his quality of life.

INELIGIBILITY FOR LT IN ACUTE ON CHRONIC LIVER FAILURE (ACLF)

ACLF is a distinct syndrome that develops as a sequela of acute decompensation of cirrhosis and carries significantly higher morbidity and mortality, driven mainly by extrahepatic organ failures. There is an unmet meet for a score that can be used to list patients with ACLF for LT. The MELD score doesn't adequately judge the non-renal organ failures and systemic inflammation, which are the drivers of morbidity and mortality in ACLF. One of the most debatable issues is ascertaining the right ACLF candidate to be transplanted. Recent times have seen an evolving role of LT in patients with ACLF.[16] Data from UNOS and CANONIC study show that patients up to ACLF grade 3 and a CLIF-C ACLF score <64 should be considered for LT.[17,18] While these studies were done using deceased donor grafts, good outcomes have also been reported in live donor programs.[19] The Asian Pacific Association for Study of the Liver (APASL) recommends that patients with MELD >28, an AARC score >10, and advanced HE in the absence of overt sepsis and multiorgan failure should be considered for LT.[20]

The timing of performing LT in ACLF is another challenge. The outcome of LT is good when done within 30 days compared to delaying it beyond 30 days.[21] APASL recommends that the first one to two weeks of ACLF are most crucial. Emergency LT is indicated if an MELD score is more than 30 with HE or bilirubin more than 22 mg/dl and if an INR is more than 2.5 with accompanying grade 3/4 HE.[22] There is data that show that the group where LT was done after the recovery of one organ failure (grade 3 to grade 2) had better outcomes than the group where there was no recovery.[23,24]

Uncontrolled culture-positive infections, severe sepsis, and invasive fungal infections are precipitants and can occur as complications of ACLF and contraindicate LT. However, patients with controlled infection can be taken for LT. A recent consensus was drawn to find factors determining the futility of LT in patients who are too sick. Thresholds of severity contraindicating LT were a PaO_2/FiO_2 ratio <150 mm Hg, a norepinephrine dose >1 μg/kg per minute, and a serum lactate level >9 mmol/L.[25]

INELIGIBILITY IN SPECIFIC AETIOLOGIES OF LIVER DISEASE

Alcoholic Liver Disease

ALD is one of the leading causes of cirrhosis. Transplantation for patients with ALD has always evoked debate due to the risk of return to harmful drinking. A meta-analysis estimated this risk to be 4.7% per year for any alcohol use and 2.9% for severe relapse.[26,27] Long-term survival may be affected by alcohol relapse, and recurrent alcoholic cirrhosis develops in one-third of patients with severe relapse.[27] There may also be a bias against the transplantation for ALD with ethical concerns of LT for a self-inflicted illness. It has been perceived that patients with a history of alcohol abuse will make poor transplant candidates, and it has been estimated that 95% of patients with end-stage ALD are not referred for the evaluation for LT.[28]

However, the outcomes of LT for ALD have been reported to be similar to those of other causes of liver disease.[29] The graft loss due to recidivism after LT has been reported to be similar to primary biliary cirrhosis, about 2% by 10 years.[30] Some French LT centers analyze blood alcohol on the day of LT admission if there is doubt of sobriety. However, a positive test does not always result in the patient being discarded for the fear of losing a potential life-saving graft. A recent study from France showed that alcohol consumption on the day of LT for alcohol-associated liver disease, detected by positive blood and/or alcohol levels on the day of LT, did not affect long-term survival.[31]

Traditionally, a 6-month abstinence rule had been followed before the consideration of a patient with ALD for LT. This 6-month rule was considered as it gave enough time for the liver to recover on abstinence and avoid unnecessary transplant. Moreover, it gave a reasonable length of time to assess the patient's commitment to abstinence. However, this 6-month rule was not based on robust data, and many groups have advocated earlier transplantation for patients with severe ALD. The arguments in favor of earlier LT are that the length of abstinence is not related to the risk of recidivism, most of the recovery occurs in the first three months, and many patients with severe ALD will die before the 6-months period is over. In severe alcoholic hepatitis with Maddrey's score >32, with the failure of response to steroids, and a Lille score >0.45, the expected survival at 6 months is below 30%.[32] Mathurin *et al.*[33] showed that in patients with severe alcoholic hepatitis who did not respond to steroids, selected patients with supportive family members, no severe coexisting conditions, and a commitment to alcohol abstinence had good survival with a low risk of recidivism. Patients with ALD who fail to improve after abstinence should be considered for LT. Duration of sobriety should not be the sole criterion to decide on the fitness for LT.

Patients of ALD being assessed for LT should undergo psychological assessment for commitment to abstinence and family support before listing for LT. Patients who do not show commitment to abstinence, have poor family support, or have concomitant drug abuse should not be considered for LT. Recently, Lee *et al.*[34] have developed

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the SALT score, a prognostic score which uses four objective pre-LT variables and identifies patients with alcoholic hepatitis who are at low risk of post-LT recidivism. Variables include more than 10 drinks per day at initial hospitalization (4 points), multiple prior rehabilitation attempts (4 points), alcohol-related legal issues (2 points), and illicit substance abuse (1 point). Patients with a score more than or equal to 5 have a 25% PPV and 95% NPV for sustained alcohol use post-LT and should be avoided as recipients for LT.

Hepatitis B

There has been a recent decline in the number of LT for decompensated hepatitis B virus (HBV)-related cirrhosis.[35] Factors responsible are highly effective HBV vaccine and potent drugs with a high barrier of resistance. Treatment with nucleoside analogs and with a high barrier of resistance (entecavir or tenofovir) leads to improvement in the liver function, which in turn is reflected in the rise in the mean age of decompensated HBV patients who are on the waiting list and undergo transplant.[35] Also, in the current era, HCC instead of the decompensation of liver disease has become the most common indication for LT in chronic hepatitis B.[35]

An acute flare of chronic hepatitis B is a commonly encountered clinical scenario, which can occur spontaneously in the natural life cycle of infection or result from cancer chemotherapy/immunosuppressive treatment. The patient's prognosis is determined by both the severity of the flare and the baseline fibrosis due to HBV. These patients can present with an ACLF-like presentation and sometimes have very high short-term mortality. Data are sparse on the optimal timing of LT in these patients. A recent study showed the usefulness of the MELD score for deciding the future course. The authors found that mortality was high (>50%) in MELD $\geq$32 compared to lower mortality (<25%) in patients with MELD $\leq$28. In patients with MELD between 28 and 32, mortality was high if patient had three to four at-risk criteria (age $\geq$52 years, alanine aminotransferase $\geq$217 U/L, baseline platelet levels $<127 \times 10^9$/L, and the presence of cirrhosis/splenomegaly/ascites on imaging).[36] Patients with HBV flare who have mild disease should be considered ineligible for LT and should be managed expectantly with nucleoside analogs before considering LT. On the other hand, early LT should be considered in patients with MELD $\geq$32 or in patients with a MELD score between 28 and 32, if they are older, have high transaminases, and the imaging shows confirmed cirrhosis with a shrunken liver, ascites, or splenomegaly.

Hepatitis C

Hepatitis C was one of the most common indications for LT in the past. However, with the advent of directly acting antiviral agents (DAA), there has been a decline in LT for HCV-related liver disease.[37,38] The presence of detectable RNA at the time of the transplant is not a contraindication to LT. The primary goal of treatment before LT is to prevent HCV recurrence, which almost always occurs if HCV RNA is detectable at the time of LT. The secondary gain of therapy is that the hepatic function significantly improves after treatment with DAA therapy of patients, which sometimes can lead to delisting. The probability of delisting is around 35% (MELD < 16), 12% (MELD = 16–20), and 5% (MELD > 20) based on the severity of the liver disease.[39,40] Also, treating before LT, drug interactions are less compared to post-LT period, and lastly, treatment is the only option for patients where LT is not available. There are a few caveats about treating before LT. Firstly, the SVR rates are lower than those attainable when treating after LT. Secondly, it is vital to understand the concept of "MELD limbo" or "MELD purgatory," where, although the MELD score improves, patients keep suffering from a reduced quality of life and complications of end stage liver disease (ESLD) like HCC.[41] Data show that benefits with therapy before LT are limited to patients with MELD less than 20, with approximately 20% of patients getting delisted after 60 weeks after the start of treatment.[39,42] Considering these factors in mind, the European Liver and Intestine Transplant Association and the International Liver Transplantation Society consensus statements recommend that patients with MELD >25 (more so if >30) and those who are likely to receive LT within three months should not be treated before LT.[40,43] Patients with MELD less than 20 should be treated with DAA before considering LT.

Autoimmune Liver Disease

AIH is an immune-mediated inflammatory liver disease of unknown etiology. The condition can present as asymptomatic transaminitis, acute severe hepatitis (AS-AIH), ACLF (AIH-ACLF), decompensated cirrhosis and its complications, or ALF (AIH-ALF). The 10- and 20-year transplant-free survival with currently available treatment options is around 90 and 70 percent, respectively.[44] The management of patients having AS-AIH (defined as presentation in the form of jaundice, an INR > 1.5 < 2, no encephalopathy, and no previously recognized liver disease) or AIH-ALF is still controversial.[45] The advantages of steroid treatment must be balanced against the risk of infections[46] and a delay in LT.[47,48] In patients having AS-AIH on corticosteroid treatment, it is very important to identify factors that predict non-response to therapy, as, if delayed, a patient can rapidly progress to ALF and or sepsis. There is a narrow therapeutic window of 1–2 weeks to judge response to steroids. Patients who do not respond to therapy and have persistently raised bilirubin, clinical deterioration, or the development of encephalopathy should be

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considered for immediate LT.[45,47–50] Recent data have shown a promising role of the SURFASA score with a cut-off point of −0.9. It is a dynamic score in which an INR at the introduction of steroids and the evolution of an INR and bilirubin after 3 days are predictive of LT or death.[51] Patients of AIH-ALF are very sick and there is inadequate time for waiting for steroid response. These patients usually require early LT as a life saving measure. AIH-ACLF is a well-recognized entity and recent data show the importance of an early biopsy in identifying this subset, as like AS-AIH, many of them are seronegative. Patients with advance age, higher MELD (more than 27), concomitant hepatic encephalopathy, and a higher grade of fibrosis (≥3) were found to have poor response to steroid therapy and hence, helps in identifying the subset which will require LT.[52] Patients with AIH with milder disease should be ineligible for the transplant unless there is a lack of response to steroid therapy.

Budd Chiari Syndrome

BCS is a rare disease characterized by the obstruction of the hepatic venous outflow anywhere from the intrahepatic venules to the supra-hepatic portion of the inferior vena cava. It can manifest in a spectrum ranging from asymptomatic disease to cirrhosis and its complications, fulminant hepatic failure, and even HCC. If untreated, the prognosis is dismal, with 50% survival at 2 years and less than 10% survival at 3 years. This is due to rapid liver fibrosis because of congestion.[53]

Patients with BCS should be considered for other options before LT. Anticoagulation, diuretics, and transjugular intrahepatic portosystemic shunting or portosystemic shunt surgery are the available treatment options that are used in a stepwise manner. The use of this stepwise approach results in good long-term outcomes in the majority of patients. Although the data are heterogeneous, the 5-year survival with transjugular intrahepatic portosystemic shunting in patients of BCS is reported to be between 56 and 88%.[54] However, 10–20% of patients will not respond to this stepwise management and will require LT. In a large study, the 1-, 3-, and 5-year survival reported after LT for BCS was 76%, 75%, and 72%, respectively. Renal failure and the presence of a shunt were independent predictors of patient survival.[55]

Fulminant BCS is a rare entity described in case reports and series, which leads to ALF and responds poorly to medical management. A stepwise approach, which is shown to improve the outcome in BCS patients, is unlikely to succeed in ALF due to BCS, and emergency LT remains the only viable option. A recent paper from Alukal *et al.*[56] is the largest data comparing outcomes after LT in fulminant BCS and BCS patient being treated in a stepwise manner and eventually requiring LT as a last resort. The authors found that BCS patients undergoing emergency LT had an excellent survival. BCS patients are usually ineligible for LT unless there is a failure of stepwise therapy, the management of BCS patients with ALF is often based on an expert opinion rather than standard guidelines. However, data from the above study suggest that patients in ALF due to BCS should be considered for expedited LT.

Cholestatic Liver Disease

Autoimmune cholestatic liver diseases are debilitating conditions with significant morbidity and impairment in life. Unlike the indications of LT in routine etiologies of ESLD discussed above, pruritus can be severe and distressing, and LT is often considered for quality of life issues at stages where liver functions are relatively preserved compared to other causes of CLD.[57] Primary biliary cholangitis (PBC) is an autoimmune liver disease that leads to slow and progressive injury to small intralobular bile ducts. Several risk stratification scores and criteria have been developed to predict transplant-free survival and response to therapy in PBC, including Paris-I and II, Barcelona, Rochester, Rotterdam, and Toronto criteria.[58–63] The Mayo disease model is the most widely accepted and used among all these. Patients need to be evaluated for LT if the predicted one-year survival is less than 95%, corresponding to scores more than 7.8 when calculated using the Mayo Model. Hence, this cut-off is the ideal time to consider patients for LT.[64]

As for PBC, multiple prognostic models have been described in the literature to predict transplant-free survival in primary sclerosing cholangitis (PSC), which include the Mayo Clinic model, King's College model, the multicenter model, and the Amsterdam–Oxford model.[65–68] Although these models are cumbersome, they facilitate patient selection timing of LT by calculating predicted survival with readily available post-LT survival rates. The revised Mayo model is the most widely used one.[69] Patients with PSC receive additional MELD points if they develop two episodes of culture-proven bacteremia within 6 months or non-iatrogenic cholangitis in patients without a structural lesion or a biliary stent. Patients with cholestatic disorders who do not meet these criteria should be considered ineligible for transplant. There are, however, a few limitations of the models as they do not take into account the development of cholangiocarcinoma and variceal bleeding, which can adversely affect the prognosis in PSC patients.

Inherited and Metabolic Liver Disease

Inherited disorders that affect the liver manifest in predominantly two forms. There can be a predominant liver involvement as in Wilson's disease, hereditary hemochromatosis, tyrosinemia, and alpha-1-antitrypsin deficiency. On the other hand, there can be predominant extrahepatic manifestations with normal liver architecture as in urea

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cycle disorders, Crigler-Najjar syndrome, familial amyloid neuropathy, primary hyperoxaluria type 1, and atypical hemolytic uremic syndrome-1.

Patients with Wilson disease are considered for LT when they develop ESLD with complications of cirrhosis and in the presence of Wilsonian ALF. Assessing drug compliance and the appropriate dosage of chelating agents is vital. Another important aspect of evaluating patients for LT is neurological damage due to disease. Long-standing advanced neurological illness is unlikely to improve and can instead worsen after LT. Primary hemochromatosis is a rare disorder and, if detected early, timely phlebotomy can avoid LT. The pressing issue in patients undergoing LT is an iron overload in systemic organs like the heart and pancreas manifesting as cardiomyopathy and diabetes. Outcomes following LT are worse than other disorders, with infections and cardiac complications contributing to mortality.

TRANSPLANTATION FOR CIRRHOSIS IN SPECIFIC CIRCUMSTANCES

Elderly

Recent studies have shown the feasibility of LT in the elderly, and although a precise cut-off age doesn't exist, a trend towards 70 years is being seen.[70,71] A recent meta-analysis did not find any difference in the outcomes between the young and the elderly.[72] It is important to screen the elderly for comorbidities and cancer before considering LT. Screening colonoscopy for recipients more than 50 years of age is advisable. Nutritional assessment, including sarcopenia evaluation, is essential. The best surrogate measure is psoas muscle thickness on a CT scan. It is vital to evaluate for frailty before LT. Frailty index is an important tool and has a role in predicting mortality.[73,74]

Metabolic Syndrome and Obesity

Non-alcoholic fatty liver disease and non-alcoholic steatohepatitis related cirrhosis is the fastest growing indication for LT, ranking second in the USA after HCC and comprising around 8.4% of total LT performed in Europe.[75,76] It is very important to evaluate the associated comorbidities like diabetes mellitus, coronary artery disease (CAD), hypertension, obesity, and dyslipidemia, which can have a significant impact on surgical outcomes.[77] Many potential candidates are rendered unfit as they have high surgical risk.

Obesity management forms a cardinal part of pre-LT workup. Although traditionally defined using BMI, it is an imperfect method in patients with ESLD. Firstly, ascites has a bearing on the calculation of BMI, and sarcopenia is a better predictor of post-LT outcomes. Secondly, sarcopenic obesity, defined as sarcopenia with excess visceral fat, is associated with increased mortality. Another area of concern is to obtain an acceptable graft-to-recipient weight-ratio for obese patients. Current guidelines consider morbid obesity (BMI > 40) as a relative contraindication for LT.[78] The foremost reason being a poor post-LT outcome due to the higher risk of infectious, cardiovascular and respiratory complications. These patients often require longer hospital stay and increased resource utilization.[79]

The timing should ideally be at least a year before planned LT so that adequate duration is available to achieve weight loss and its benefits.[80] Sleeve gastrectomy is the preferred option as access to the biliary system is preserved, there is minimal effect on drug pharmacokinetics, and there is access to the stomach in cases of gastric variceal bleeding. A decision to transplant if BMI >35 should always be taken by a multidisciplinary team, including a dietician, psychologist, hepatologist, anesthetist, and surgeon.[80]

Cardiovascular Co-morbidity

Cardiovascular assessment is also very crucial in patients of non-alcoholic fatty liver disease before LT as many LT candidates are older and have non-alcoholic steatohepatitis and metabolic syndrome. CAD is present in approximately one-fourth of the LT candidates.[81] These patients may also have cirrhotic cardiomyopathy, portopulmonary hypertension (PoPH), or valvular heart disease.

Detection of CAD and appropriate cardiovascular revascularization is vital to improve post-transplant survival.[82,83] The Cardiovascular Risk in Orthotopic Liver Transplantation (CAR–OLT) score was developed to quantify the risk for intraoperative and immediate postoperative cardiovascular disease events after LT.[84] Patients with CAD who undergo coronary stenting need dual antiplatelet therapy. The current recommendation is to wait a minimum of 1 month after bare metal and 6 months after drug-eluting stent stenting before LT.[85] Patients with significant CAD who need early LT can either undergo coronary revascularization with bare metal stents, undergo coronary artery bypass grafting before LT, or a combined LT and cardiac surgery. Non-revascularized obstructive severe multivessel CAD is an absolute contraindication for LT.[86] A recent paper from Rachwan *et al.*[87] has simplified the evaluation of CAD in patients being worked up for LT using the CAD-LT score. The score divides patients into three categories, low risk, intermediate risk, and high risk. The high-risk group (CAD-LT score ≥9) straight away proceeds to conventional angiography and it identifies significant CAD with 97% sensitivity. The low-risk group (CAD-LT score ≤3) doesn't need further cardiac evaluation prior to LT. The intermediate risk (score 4–8) proceeds for a non-invasive evaluation, which further stratifies the patient into low-risk intermediate (score 4–6) and high-risk intermediate (score 7–8). The low-risk intermediate doesn't require a further workup, however, the high-

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Table 3 Special Considerations for LT in Different Etiologies.

	Considerations for transplantation	Transplant ineligibility
Acute Liver Failure	Kings's college criteria ALFED model	Severe sepsis with positive blood cultures, significant hypotension despite high-dose ionotropic support, brain herniation, or brain death are contraindications to LT
ACLF	**APASL criteria** Listing – MELD >28, AARC score >10, and advanced HE Emergency LT – MELD >30 with HE or Bilirubin >22 mg/dl, INR >2.5 & grade 3/4 HE **NACSELD/CANONIC criteria** ACLF grade 1, 2: List and transplant if no improvement in 7–10 days ACLF grade 3: Avoid in very sick patients CLIF-C ACLF score <64	**Avoid LT if** 1. PaO_2/FiO_2 ratio <150 mm Hg 2. Norepinephrine dose >1 μg/kg per minute Serum lactate level >9 mmol/L
Alcoholic Hepatitis	**Severe alcoholic hepatitis**: Day 7 Lille score >0.45	- Mild disease - Not committed to abstinence - Poor family support - Concomitant drug abuse
Hepatitis B Flare	- MELD >32 or - MELD between 28 and 32 with older age, high transaminases, and imaging shows confirmed cirrhosis with a shrunken liver, ascites, or splenomegaly	HBV flare with milder disease
Hepatitis C	- MELD >25: treat HCV after LT - MELD 20–25: treat if waitlist >3 mths - MELD <20: treat before LT	MELD <20 could be treated with DAA before considering LT
AIH	**Acute severe AIH** (INR > 1.5) – no response to steroids for 1 week	Milder AIH
HVOTO	Intractable ascites Fulminant BCS No response to medical plus interventional radiological therapy	Response to medical and interventional therapy (angioplasty ± stenting ± TIPSS)
PBC	**Intractable pruritus**: Mayo score around 7.8	Pruritus controllable No decompensation
PSC	**Cholangitis:** Two episodes of culture-proven bacteremia within 6 months or non-iatrogenic cholangitis	Pruritus controllable No decompensation No cholangitis
Wilson	Acute liver failure presentation	Response to chelation therapy
NAFLD	As per MELD status	Significant comorbidities (obesity, CAD)

Abbreviations: AARC, APASL ACLF research consortium; ACLF, acute on chronic liver failure; AIH, autoimmune hepatitis; APASL, Asia pacific association for study of liver; CAD, coronary artery disease; CLIF-C, Chronic Liver Failure Consortium; HE, hepatic encephalopathy; HVOTO, hepatic venous outflow tract obstruction; INR, international normalized ratio; LT, liver transplantation; MELD, Model for End-stage Liver Disease; NACSELD, North American consortium for study of end stage liver disease; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; TIPSS, transjugular intrahepatic portosystemic shunt.

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risk intermediate requires another non-invasive modality to assess CAD or conventional angiography.

Patients with cirrhotic cardiomyopathy have blunted inotropic and chronotropic responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities in the absence of other known cause of cardiac disease.[88] While left ventricular dysfunction is not an absolute contraindication for LT, most centers restrict LT to patients with ejection fraction (EF) >40%. However, some high-volume centers also carry out LT with ejection fraction <40%.[86]

PoPH should be suspected on echocardiography if there is an enlarged right ventricle, significant tricuspid regurgitation, and a right ventricular systolic pressure is >40–50 mmHg. An estimated right ventricular systolic pressure of >40–50 mmHg on transthoracic echocardiography is an indication of right heart catheterization.[89] In patients with POPH, right heart catheterization shows: (i) a pulmonary capillary wedge pressure ≤15 mm Hg, (ii) a mean pulmonary arterial pressure (MPAP) >25 mm Hg, and (iii) pulmonary vascular resistance (PVR) >240 dynes s cm^{-5}. There is high mortality after LT in moderate and severe PoPH. Krowka *et al.*[90] found that a pre-LT MPAP of ≥50 mm Hg was associated with 100% cardiopulmonary mortality, and an MPAP of 35–50 mm Hg and PVR of ≥250 dynes s cm^{-5} was associated with a mortality rate of 50%. Pulmonary vasodilator agents may allow successful preoperative optimization of the MPAP to ≤35 mm Hg, allowing liver transplantation. LT should be avoided in severe PoPH, which is unresponsive to vasoactive medication (MPAP <35 mm Hg and PVR <400 dynes s cm^{-5}).[86]

Stenotic valvular heart lesions cause pressure overload and hypertrophy of the left ventricle and decreased left ventricular compliance, resulting in significant hemodynamic instability, ischemia, and life-threatening arrhythmias during LT. LT should be avoided in severe aortic stenosis unless a preoperative valve repair or a transcatheter aortic valve replacement is carried out or a combined LT and cardiac surgery is done.

Congenital heart disease can be associated with increased right heart pressures, which may affect the hepatic function and a combined heart and LT may need to be carried out.

Hepatopulmonary Syndrome (HPS)

The International liver transplant society recommends the European Respiratory Society Task Force diagnostic criteria for diagnosing HPS.[91] HPS is classified into mild (PaO_2 ≥ 80 mm Hg), moderate (PaO_2 = 60–79 mm Hg), severe (PaO_2 = 50–59 mm Hg), and very severe (PaO_2 < 50 mm Hg). As per the guidelines, severe hypoxemia should be considered an indication of LT and such individuals should have expedited LT consideration. Patients in the very severe category have a markedly high incidence of complications and death after LT.

Renal Dysfunction and Assessment for SKLT

Patients of CLD with renal dysfunction should be assessed for the need of simultaneous kidney and LT rather than straight away carrying out LT. Renal dysfunction is common in ESLD and comprises a spectrum from acute kidney injury (AKI) and hepatorenal syndrome to chronic kidney disease (CKD) requiring dialysis. Recent guidelines from the Organ Procurement Transplant Network Criteria recommend considering simultaneous kidney and LT in CKD when (i) a glomerular filtration rate (GFR) <60 ml/min for >90 days and a subsequent GFR <30 ml/min or requirement for dialysis and (ii) CKD because of metabolic disease that can be corrected with a liver transplant (hyperoxaluria, atypical hemolytic uremic syndrome, familial non-neuropathic systemic amyloidosis, and methylmalonic aciduria). Criteria for SLKT allocation in the setting of AKI include (i) duration of AKI >6 weeks with a persistent GFR <25 ml/min, (ii) dialysis dependence, or (iii) a combination of both.[92]

It is important to note that a patient with hepatorenal syndrome not meeting the above AKI criteria should not undergo SLKT and should be taken up for LT alone. There is a safety net option where, if the renal function doesn't improve after LT, the patients can be listed for an expedited kidney transplant.[92] However, these guidelines have a role in the setting of DDLT where organ procurement is controlled by a nation-wide program like USA. In India, where majority of LT is LDLT, routine contraindications of LT apply to SLKT.

Hepatocellular Carcinoma

HCC is the most common reason for performing LT in the USA and accounts for 20–40% of total LT performed. The landmark study by Mazzaferro proposed the widely accepted Milan criteria that have since been used for selecting patients for LT.[93] Multiple other criteria, including UCSF and extended Toronto, have been proposed (Table 3).[94–98] Recent papers suggest that tumor biology also has an important role in predicting post-LT recurrence and survival, with alpha-fetoprotein levels >1000 ng/ml, even if within Milan criteria, predicting poor outcome.[99]

Locoregional therapies (LRT) available to target HCC include transarterial chemoembolization, radiofrequency ablation, transarterial radioembolization, microwave ablation, radioembolization, stereotactic body radiotherapy, and/or hepatic resection. Tumor downstaging refers to the use of LRT to reduce tumor burden, enabling HCC to meet the criteria used for listing for LT. Data also show the promising role of downstaging therapy to reduce excessive tumor burden to bring patients within acceptable criteria for LT.[100–102] There is no definite agreement on the

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Table 4 Decision Making to Account for Physical Status and Comorbidities.

	Indication	Special circumstances/considerations
Age	<60 years	Proceed for LT
	60–70 years	Detailed assessment of comorbidities Sarcopenia assessment Cancer screening – Colonoscopy, PSA
	>70 years	Depends on overall health (varies case to case)
Hepatopulmonary syndrome (HPS)	Mild ($PaO_2 \geq 80$ mm Hg) Moderate (PaO_2 60–80 mm Hg) Severe ($PaO_2 < 60$ mm Hg) Very severe ($PaO_2 < 50$ mm Hg)	LT decision as per the status of liver disease Higher mortality, especially in very severe HPS
Renal disease (SLKT)	**CLD with CKD** GFR <60 ml/min for >90 days Subsequent GFR <30 ml/min Requirement for dialysis **CLD with AKI** Duration of AKI >6 weeks with GFR <25 ml/min Dialysis dependence **CKD due to metabolic disease correctable with LT**	Avoid solitary LT without renal transplantation in AKI or CLD meeting criteria for SKLT
HCC	Downstaging if outside Milan criteria	Avoid transplant if macrovascular invasion or extrahepatic metastasis
Obesity	To lose weight before transplant	Avoid if BMI >35 Consider bariatric surgery – Sleeve gastrectomy one year before LT
Cardiac disease	**CAD:** wait for 1 month after bare metal & 6 months after drug-eluting stent before LT	In patients needing early LT: bare metal stents, coronary artery bypass grafting before LT, or combined LT and cardiac surgery
	Cirrhotic Cardiomyopathy: consider LT if EF >40%	Avoid if EF <40%
	PoPH: preoperative optimization of MPAP to ≤35 mm Hg with pulmonary vasodilator agents	Avoid LT in severe PoPH which is unresponsive to vasoactive medication (MPAP <35 mm Hg & PVR <400 dynes s cm^{-5}

Abbreviations: AKI, acute kidney injury; BMI, body mass index; CKD, chronic kidney disease; CLD, chronic liver disease; EF, ejection fraction; GFR, glomerular filtration rate; HCC, hepatocellular carcinoma; HPSS, hepatopulmonary syndrome; LT, liver transplant; PaO_2, partial pressure of oxygen; PoPH, portopulmonary hypertension; SKLT, simultaneous kidney and liver transplantation.

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best modality, with transarterial chemoembolization and transarterial radioembolization being the most promising. A recent systematic review showed an overall success rate of around 48%, i.e., around half of the patients considered for downstaging ultimately undergo LT.[103] A recent study showed that normalization of alfa-fetoprotein to <20 ng/ml after LRT predicted successful downstaging and was associated with better outcomes after LT.[104]

Recent guidelines suggest using LRT for bridging therapy for T2 tumors (size between 2 and 5 cm, without a vascular invasion) within the Milan criteria on the waiting list. The rationale behind this is to reduce the dropout rate from the waiting list due to tumor extension from 15 to 25% (without bridging) to less than 10%.[105,106] Bridging therapy is recommended if the expected waitlist time is more than 6 months.[78] However, the evidence of the ideal modality to be used as bridging therapy is still scarce. A liver transplant should not be considered in HCC if there is a macrovascular invasion or extrahepatic metastasis. Decision making to account for physical status and comorbidities is depicted in Table 4.

SARCOPENIA AND FRAILTY

The prevalence of sarcopenia and frailty in cirrhosis ranges between 40–70%[107] and 18–43%, respectively.[108] Frailty is a distinct biologic syndrome of decreasing physiologic reserve and increasing vulnerability to health stressors.[109] Frailty is assessed using various tools like frailty index, a clinical frailty scale, and a hospital frailty risk score.[110,111]

Sarcopenia, defined as loss of muscle mass, has been shown to be an independent predictor of post-LT outcomes,[112] which include longer hospital/ICU stay, higher incidence of infection after LT, and higher overall health costs. Cross-sectional imaging using CT/MRI is the most well validated, accurate, and objective sarcopenia assessment tool.[113] Patients of cirrhosis having physical frailty (liver frailty index > 4.5) increases the adjusted risk of waitlist mortality.[114]

It is important to take both sarcopenia and frailty into account before considering a patient for LT. There is definitely a role of nutritional support in form of adequate calorie and protein supplementation in the vulnerable population to improve post-LT outcomes. Recent data are upcoming regarding the use of testosterone,[115] branched chain amino acids,[116] L-carnitine,[117] and, L-ornithine L-aspartate[118] for improving muscle mass in this vulnerable population.

LT is not indicated if the risk of transplant-related mortality is more than that of liver disease *per se*. Special considerations in different etiologies which may make the patient ineligible for LT are shown in Table 1. When the indication of LT is present, it is critical to assess comorbidities that will affect the patient's ability to tolerate the transplant surgery or affect long-term survival. At times, the contraindications may be temporary as it may be better to defer transplant to optimize the patients, such as in sepsis or untreated human immunodeficiency virus infection, so that the outcome of LT may be improved. Decision making to account for the physical status and comorbidities is depicted in Table 2.

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Pankaj Puri: Writing & review of manuscript; Sarthak Malik: Writing of manuscript.

CONFLICTS OF INTEREST

The authors have none to declare.

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