Liver Transplantation: Protocol for Recipient Selection, Evaluation, and Assessment☆

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Liver transplantation (LT) is the definitive therapy for patients with end-stage liver disease, acute liver failure, acute-on-chronic liver failure, hepatocellular carcinoma, and metabolic liver diseases. The acceptance of LT in Asia has been gradually increasing and so is the expertise to perform LT. Preparing a patient with cirrhosis for LT is the most important aspect of a successful LT. The preparation for LT begins with the first index decompensation for a patient with cirrhosis. Patients planned for LT should undergo a thorough screening for infections, and a complete cardiac, pulmonology, and psychosocial evaluation pre-LT. In this review, we discuss the indications and contraindications of LT and the evaluation and assessment of patients with liver disease planned for LT. (J Clin Exp Hepatol 2023;13:841–853)

Liver transplantation (LT) is the definitive treatment for patients with end-stage liver disease and acute liver failure (ALF). The first LT in humans was attempted in 1963 in Colorado, USA, by Starzl *et al.* However, the first successful human LT was performed only in 1967.[1,2] In the 1980s, LT moved to be a therapeutic approach rather than an experimental modality. The outcomes remained dismal, with a 1-year survival rate of about 25% till the invention of calcineurin inhibitors, now widely used post-LT.[3] The 1-year survival rate has improved to more than 80%, along with an improvement in overall morbidities.[4] In India, Human Organ Transplantation Act was passed in 1994, and the first successful deceased donor liver transplant (DDLT) was performed in 1998, followed shortly by the first successful living donor liver transplant (LDLT) in 1998.[5]

Data from the Indian Liver Transplant Registry (ILTR, www.iltr.org), which went live from August 2019, suggest that close to 1800 LTs are performed every year in India, in around 90–100 centers. In contrast to the Western world, where DDLT is more common, LDLT is more predominant in India.[6] Recent literature published by large-volume centers from India reports 1-year and 3-year adult survival between 80–85% and 61–75%, respectively, with viral hepatitis and alcoholic liver disease being the most common indications for LT.[6,7]

Several unique challenges loom in the field of LT in our country. The number of patients on LT wait-lists is disproportionate to the number of organs available from deceased donors. The major hindrance to LT in the Indian population is the lack of access to healthcare, indigent national policies, and financial support precluding LT.[8] Patients often present to transplant centers with high model for end-stage liver disease (MELD) scores. Multiple hospital admissions before LT increase the risk of multidrug-resistant infections and poorer outcomes post-LT.[5,9,10] Poor management of hepatitis B and hepatitis C, as well as apathy in dealing with nonalcoholic steatohepatitis (NASH), is a major contributor to late referrals. Successful public-sector transplant programs and a national registry for organ allocation are lacking. Despite several constraints, the number of private institutes performing LT, access to LT, and expertise has significantly improved in recent years.[11] A sick patient or a potentially inappropriate candidate for LT may have a survival of fewer than 3 months and is not suitable for LT.[12] Therefore, the survival of a patient post-LT is dependent on the appropriate selection of a candidate for LT. In this review, we discuss the recipient selection, evaluation, and assessment protocol.

INDICATIONS

Common indications for LT include decompensated cirrhosis, acute-on-chronic liver failure (ACLF), hepatocellular carcinoma (HCC), ALF, and metabolic liver diseases (Table 1).

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Abbreviations: ACLF: acute-on-chronic liver failure; ALF: acute liver failure; CMV: cytomegalovirus; LDLT: living donor liver transplantation; LT: liver transplantation; MELD: model for end-stage liver disease
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Cirrhosis and LT

MELD has been used to prioritize access to organs since 2002. It was initially modeled to predict the 3-month prognosis in patients undergoing a transjugular intrahepatic portosystemic shunt (TIPS) procedure.[13] LT is performed for patients with end-stage liver disease who have a survival <1 year with poor quality of life without LT. Weisner *et al.* first demonstrated the ability of MELD score to correctly rank the mortality risk of the transplant candidates and aid in appropriate prioritization.[14] Three-month mortality of those with MELD scores <9, 10–19, 20–29, 30–39, and >40 was 2%, 6%, 19.6%, 52.6, and 71.3%, respectively.[14] Implementing MELD scores reduced the median waiting time to transplant from 981 days pre-MELD to 564 days by 2007.[15] It was observed that patients with very high MELD (≥35) had comparable mortality to those with acute fulminant hepatic failure.[16] The latter are considered an exception to the MELD system and are not confound to geographical boundaries for organ procurement.[17] The Share 35 policy was launched in 2013, which ensured that cirrhotics with advanced hepatic decompensation (MELD ≥ 35) are given the same geographical access to organs as patients with fulminant liver failure.[18] With the implementation of Share 35 policy, posttransplant survival has increased; however, the reports on reduction in wait-list mortality have been contradictory, especially in racially underprivileged sections and those with HCC.[18–21] Recent guidelines from India have proposed the Clinical Severity Score as a tool for prioritizing patients with cirrhosis to LT.[22] This complex score, including modifiable clinical variables with MELD score and waiting period, requires further validation.

Modifications of MELD

There were several caveats to the initial allocation system. Serum sodium level, an easily measurable and objective variable, correlates with complications of cirrhosis, including ascites, hepatorenal syndrome (HRS), and mortality.[23] The initial study reported that for every unit decrease in serum sodium levels from 140 to 125, the mortality increases by 5%.[24] United Network for Organ Sharing (UNOS) included a cutoff from 137 and capped at 125. This reduced the wait-list mortality by 7% for each decrease in sodium levels from 137 to 125. Thus, after finding that MELD score and sodium were significant predictors of 6-month mortality in LT candidates, sodium was incorporated into the MELD score, as the "MELD-Na" score.[25] The latest modification, MELD 3.0, is the addition of female sex and serum albumin levels and capping serum creatinine to 3 mg/dl (instead of 4 mg/dl previously). The MELD 3.0 reduced wait-list mortality by reclassifying approximately 9% of individuals to a higher MELD tier, and increasing the chances of LT, especially for women[26] (Table 2).

Table 1 Indications for Liver Transplantation.

Causes	
Acute liver failure (ALF)	- Viral hepatitis- Hepatitis A (young), B, C, E (elderly) - Drug induced liver failure (Ex. ATT, CAM, Acetaminophen) - Wilson's disease - Autoimmune hepatitis - Amanita phalloides (mushroom) poisoning - Budd-Chiari syndrome - Other viruses- Dengue, EBV, CMV - Acute fatty liver of pregnancy - Hemophagocytic lymphohistiocytosis
Metabolic diseases	- Wilson's disease - Familial amyloid polyneuropathy - Primary hyperoxaluria - Cystic fibrosis - Alpha-1 antitrypsin deficiency - Glycogen storage disease (type I and type IV) - Tyrosinemia - Hemochromatosis - Acute intermittent porphyria
Chronic liver disease/ Cirrhosis due to any cause	- MELD >15 - Child B Cirrhosis with portal hypertension - Standard MELD exception points

CMV, cytomegalovirus; EBV, Epstein Barr Virus; MELD, model for end-stage liver disease; ATT, antitubercular treatment; UKELD, United KIngdom End-stage liver Disease; D-Delta MELD; HIV, Human immunodeficiency virus.

Key message: MELD scoring remains the gold standard for listing a patient for LT to date.

ALF has been covered in detail elsewhere.[27]

Acute-on-Chronic Liver Failure (ACLF) and LT

The incidence of ACLF has significantly increased in recent years.[28] Although several advances have been made in the management of these very ill patients; the outcomes remain poor in the absence of LT. Development of multiorgan failure may preclude a successful LT. Therefore, most patients with ACLF, irrespective of the etiology, should be considered for early LT to improve survival.[29] The validity of MELD score allocation system in patients with ACLF is limited. Despite having a higher median MELD-Na score, during the index admission, only 0.7% of patients with ACLF-1, 1.9% with ACLF-2, and 2.7% with ACLF-3 were considered for LT, and this increased by merely 3.5%, 7.3%, and 4.2% at 6 months.[30] A similar study reported higher wait-list mortality (33–40%) in patients with ACLF and low MELD (<25) compared to only <10% in patients with MELD scores <25 and no ACLF.[31,32] However, MELD scoring may be more valuable in patients with ACLF identified by Asian Pacific Association for the Study of Liver Disease (APASL) criteria, which is dependent mainly on liver failure.[33–35] An increase in MELD score by ≥2 points at 2 weeks can predict survival

Table 2 Modifications of MELD.

Name of MELD	Year of introduction	Modifications	Comments
MELD XI	2007	Included only creatinine and bilirubin	- Suited for those who are on anticoagulation
Integrated MELD (iMELD)	2007	Includes sodium and age	- Increased accuracy in predicting mortality
MELD Na	2008	Sodium	- Serum sodium concentration is an important predictor of survival
D-MELD	2009	Donor age x MELD score	- <1600 predicts better survival
UKELD	2011	Similar to MELD Na, in UK. Different coefficients	- UKELD >49 predicts mortality of >9% at 1 year - UKELD >60 = 50% 1 year mortality
Recalibrated MELD	2013	Multivariate model recalibration	- Predicting 6-week mortality in acute variceal bleeding
ReFit MELD ReFit MELD Na	2017	Updated coefficients, change upper and lower bounds, and incorporate serum sodium	- improved wait-list mortality prediction
MELD Na with LFI	2017	C-statistic of 0.77 to predict wait-list mortality.	- Reclassify appropriately 19% of non-delistings
MELD Lactate	2020	Lactate	- Early and objective predictor of inpatient mortality
MELD 3.0	2021	Albumin, Female sex added	- More accurate mortality prediction - Addresses sex disparity

LFT, liver frailty index; MELD, model for end-stage liver disease; Na, sodium.

at 60 days, which may be more useful in Asian settings where LDLT is commonly performed.[34,36]

Key message: Patients with ACLF should be assessed for the suitability of LT and should be sensitized regarding LT at the first visit.

HCC and LT

The incidence of HCC has significantly increased in recent years in India.[37–39] The Milan criteria are the current gold standard criteria for listing HCC patients for LT.[40] Mazzaferro *et al.* reported that 4-year survival was 75%, with less than 10–15% recurrence, when LT was performed in early HCC: one nodule ≤5 cm or ≤3 lesions, none >3 cm and absence of gross vascular invasion, metastases or lymph nodes involvement.[41] The American Association for the Study of Liver Disease (AASLD) recommends bridging therapy in patients awaiting LT, who meet the Milan criteria.[42] These include modalities like liver resection, percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), transarterial chemoembolization (TACE), radioembolization, and radiotherapy. Some of these techniques are also used to "downstage" HCC, that is, reducing the tumor burden such that it can meet the criteria for LT. The recurrence of HCC after LT is as high as 20%.[43] Patients with HCC usually present late in India, and LT in selected patients is associated with overall survival comparable to that with other indications for LDLT.[44] Currently, Liver Transplantation Society of India (LTSI) suggests performing LT for patients satisfying the University of California, San Francisco (UCSF) criteria (single tumor ≤6.5 cm or ≤3 tumors with the largest tumor diameter ≤4.5 cm and total tumor diameter ≤8 cm) with AFP <1000 ng/ml and no major vascular invasion or extrahepatic spread.[22,45] Several other models, including the French AFP model, the Metroticket 2.0 model, and Kyoto criteria, have included surrogates of tumor biology like AFP and Des-gamma-carboxy prothrombin (DCP) to reliably predict negative post-LT outcomes; however, the universal use of such criteria are lacking.[46]

Metabolic Syndromes and LT

LT can be curative and/or lifesaving for various inherited diseases of the liver. Metabolic liver disease is not an uncommon indication for LT in India. These include conditions such as Wilson disease, glycogen storage disorders, hemochromatosis, tyrosinemia, and urea cycle defects. The presence of extrahepatic manifestations in metabolic diseases has been shown to affect survival post-LT in all ages.[47] Excellent long-term outcomes can be achieved with careful patient selection, especially since these conditions, though they remain a minor indication for LT in adults, are common indications in children.[48] Dietary management of metabolic diseases is as important as LT and must not be ignored.[49,50] One major Indian center reported 1-year and 5-year survival of 95% and 97% in the pediatric LT recipients.[29]

CONTRAINDICATIONS FOR LT

Although there are several indications for LT, there exist few conditions when LT is contraindicated. Frequent reasons for the delaying LT are active sepsis and

Table 3 Proposed Pre-LT Workup.

Blood	- Complete blood count with differential - Complete metabolic panel - Coagulation panel (PT/INR, APTT, serum fibrinogen levels) - Blood group cross match/typing - Serum calcium, vitamin D, magnesium - Tumor markers: Serum alpha-feto protein (AFP), CEA, CA19-9, PSA (for males) - G6PD testing
Endoscopic procedure	- Gastroscopy - Colonoscopy (for rectal varices and colonic ca screening)
Infectious diseases workup	- HIV - Hepatitis panel (HAV IgG, HBsAg, Hbcore total, Anti HCV), - Rapid plasma reagin for syphilis - Cytomegalovirus (CMV) IgG and IgM. - Epstein Barr Virus (EBV) IgG - Herpes simplex virus serology
Imaging	- Contrast enhanced computed tomography (CECT) - Magnetic resonance cholangiopancreatography (MRCP) - PET-CT (for HCC patients) to rule to metastasis - Mammography for females
Cardiac	- ECG, Transthoracic echocardiography, - Dobutamine stress test - CT or conventional Coronary angiography (when indicated) - Right heart catheterization (for PoPH)
Endocrinology	- Thyroid profile, lipid profile - HbA1C, fasting and post-prandial sugars
Pulmonology	- Arterial blood gas analysis - Chest x ray, pulmonary function test - CT thorax (in select cases)
Renal	- Complete urine examination - 24 h urine protein - Creatinine clearance test - USG with doppler studies of kidney (can also evaluate prostate size)
Gynecology	- USG pelvis - Pap smear - Urine pregnancy test
Neurology	- CT or MRI brain for ALF (if feasible) and for those individuals with history of TIA/CVA - EEG for those with history of seizures - Carotid doppler (in high-risk individuals)
Psycho-social evaluation	- Support system and caregiver assessment - Drug/Tobacco/Alcohol dependence assessment
Sarcopenia work up	- Liver frailty index - Bone mineral density - CT L3 skeletal muscle index - Bioimpedance analysis - Nutritional assessment
Other	- Age appropriate cancer screening - Oral health - Financial counseling

dyselectrolytemia, especially hyponatremia. Age itself is not a criterion to exclude patients from LT candidacy. Studies comparing outcomes in the geriatric population (70 years and older) have shown comparable mortality and graft function outcomes.[51,52] However, patients with severe cardiopulmonary diseases who have a disproportionately elevated perioperative risk might not be eligible for further detailed testing. Patients with more than four organ failures are also not candidates for LT.[53] Terminal hepatic encephalopathy (HE), presenting as brain death, is nonreversible and is an absolute contraindication to LT, while other stages of encephalopathy can be reversed with LT, including stage IV HE.[54] Furthermore, patients with intracranial bleeding have a dismal prognosis and should not be offered LT.[55] Other factors that exclude patients at the offset and need further work include ongoing substance use disorders and lack of adequate social support. These issues can be addressed with extensive counseling, and patients should be encouraged to follow-up.

Preparing a patient for transplant: Pretransplant evaluation

Pretransplantation evaluation usually begins when the patient is referred to a hepatology clinic when their MELD score is >15. All essential blood work should be obtained, including a complete blood count with differential, comprehensive metabolic panel, urinalysis, coagulation panel, blood group cross-matching, and typing. Additional lab work includes calcium, vitamin D levels, serum alpha-fetoprotein, and other tumor markers and infectious diseases serology (discussed further). Imaging tests are done to identify liver lesions and biliary and vascular anatomy (Table 3). Basic evaluation includes cardiopulmonary evaluation and assessment, infectious diseases workup, vaccinations, a psychosocial evaluation, evaluation of varices, and bone density evaluation. An extensive evaluation is required before LT. However, in emergency settings such as ALF and ACLF, a minimal evaluation, including basic biochemical tests, ultrasonography of the abdomen, cardiac evaluation (electrocardiogram, echocardiography), and pulmonary evaluation (chest X-ray, computed tomographic scan), are sufficient. Patients with ALF should be evaluated for irreversible neurological damage through clinical (pupil reflexes, optic nerve sheath diameter, papilledema, decerebrate posture) and radiological methods to prevent futility.

ALF, acute liver failure; aPTT, activated partial thromboplastin time; CA, carbohydrate antigen; CEA, carcinoembryonic antigen; CVA, cerebrovascular accident; EEG, electroencephalogram; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; PET-CT, positron emission tomography-computed tomography; PoPH, portopulmonary hypertension; PSA, prostate-specific antigen; PT/INR, prothrombin time/International normalized ratio; TIA, transient ischemic attack; USG, ultrasonography.

Cardiology Evaluation

Cardiopulmonary evaluation begins with an electrocardiogram. Revised Cardiac Risk Index (RCRI) is a tool to predict cardiac events postsurgery, which includes six factors (elevated risk surgery, history of ischemic heart disease [IHD], congestive cardiac failure, cerebrovascular disease, insulin-dependent diabetes, and serum creatinine level >2 mg/dl). LT is regarded as an elevated-risk surgery, which automatically puts the 30-day risk of death, myocardial infarction (MI), or cardiac arrest at 6% per the RCRI, even in the absence of other risk factors. Furthermore, the prevalence of coronary artery disease in the cirrhosis population is at least as much as in the general population.[56] Noninvasive evaluation with echocardiography is undertaken in all patients being considered for LT. Cardiac stress testing (pharmacological or exercise testing) is required for patients older than 40 years of age and in patients with multiple (≥3) risk factors for coronary artery disease in younger patients. These risk factors include a history of diabetes, history of coronary artery disease, left ventricular hypertrophy, smoking, hypertension, and hyperlipidemia. When cardiac catheterization is indicated, it carries a higher risk of bleeding due to impaired coagulation and acute kidney injury (AKI) due to concomitant renal dysfunction in these patients.[57,58] Revascularization with percutaneous coronary intervention can be safely performed, provided there is a strong indication.[58,59] Given the need for dual antiplatelet therapy in the setting of coagulopathy in these patients, bare-metal stents are preferred. It is suggested to wait for a month poststenting for LT. Additionally, a multivessel disease requiring coronary artery bypass graft has more risks and is a relative contraindication for LT.

Cirrhotic cardiomyopathy in patients with chronic liver disease is common, with a prevalence of approximately 50%.[60] It is defined by impaired cardiac function at rest, impaired contractility, and systolic and diastolic dysfunction in the absence of other known causes of cardiac disease. Other supportive criteria include electrophysiological abnormalities, abnormal chronotropic response, electromechanical uncoupling/dyssynchrony, prolonged QTc interval, enlarged left atrium, increased myocardial mass, increased NT pro-brain natriuretic peptide (NT pro-BNP), or increased troponin.[61,62] Cirrhotic cardiomyopathy is associated with significant morbidity and mortality.[60] However, cardiac dysfunction is not related to the severity of liver disease. New York Heart and the American Heart Associations (NYHA, AHA) recommend a complete cardiovascular disease workup, and the AASLD recommends a transthoracic echocardiography in all LT candidates. Expected findings in cirrhotic cardiomyopathy include prolonged QT interval, reduced exercise tolerance, alteration of aerobic capacity (peak VO_2) or ventilatory efficiency (VE/VCO_2), systolic dysfunction (ejection fraction <55%), diastolic dysfunction, left ventricular hypertrophy, diastolic dysfunction, reduce contractile reserve, and elevated NT-proBNP levels.[63] Cirrhotic cardiomyopathy reverses after LT in 6–12 months; however, the risk of heart failure with preserved ejection fraction is high in the postoperative period and merits appropriate identification before LT and management post-LT.[60]

Pulmonology Evaluation

Lung function evaluation before transplant requires clinical assessment and further testing with pulmonary function tests. Measurement of pulse oxygen saturation (SpO_2) by oximetry is essential to screen for hepatopulmonary syndrome and is a component of the ARISCAT (Assess Respiratory Risk in Surgical Patients in Catalonia) Risk Index for predicting pulmonary complications postsurgery. The Gupta calculator for predicting postoperative respiratory failure (requiring mechanical ventilation >48 h after surgery or unplanned intubation within 30 days of surgery) includes the preoperative functional status of the patient, American Society of Anaesthesiologists (ASA) class, systemic inflammatory response syndrome (SIRS) or sepsis, and elective or emergency surgery.[64]

Hepatopulmonary syndrome (HPS) is an MELD exception according to the UNOS policy, with an exception score of 22. It is caused by pulmonary vascular dilation resulting in defective arterial oxygenation. An SpO_2 ≤96% is >90% sensitive and >80% specific to diagnose moderate to severe HPS.[65] It is defined by the partial pressure of oxygen <80 mm Hg or alveolar-arterial oxygen gradient ≥15 mm Hg while breathing ambient air and transthoracic contrast echocardiography (TTCE) showing an intrapulmonary shunting. Approximately 4–32% of patients evaluated for LT have HPS, and there is a lack of concordance between the severity of liver disease and HPS. Severe HPS is a high-risk factor for prolonged postoperative ventilation, fluid overload, and mortality up to 50% in the early postoperative period.[66] HPS is reversed by LT. Restrictive fluid therapy, nitric oxide, and Trendelenburg position are recommended to prevent complications in the postoperative period.

Factors affecting overall pulmonary outcomes include age, severity of asthma, smoking, obesity, obstructive lung disease, interstitial lung disease, and pulmonary hypertension.[67] Portopulmonary hypertension (PoPH) is defined as an elevated mean pulmonary artery pressure (MPAP) of ≥25 mmHg, elevated pulmonary vascular resistance (PVR) ≥240-dynes s cm^{-5}, and pulmonary capillary wedge pressure (<15 mmHg) in the presence of portal hypertension. All LT candidates with unexplained dyspnea and/or hypoxemia should undergo transthoracic echocardiography (TTE).[68] Elevated estimated right ventricular systolic pressure (RVSP) warrants right heart catheterization (RHC) to confirm MPAP. AASLD recommends RHC

for RVSP ≥45 mmHg and/or other evidence of elevated MPAP on TTE, while the European Respiratory Society Task Force suggests a cutoff of RVSP ≥50 mmHg for RHC.[69,70] Moderate (MPAP ≥35 mmHg) and severe PoPH (MPAP ≥45 mmHg) are associated with worse mortality rates in LT patients.[71] PoPH can be treated with vasodilators to reduce the MPAP <35 mmHg and make patients eligible for LT. Tricuspid annular plane systolic excursion (TAPSE), a simple method evaluated through TTE, can help evaluate RV dysfunction. A TAPSE <1.8 cm predicts mortality in PoPH. Lastly, hepatic hydrothorax (HH) is common in patients with advanced cirrhosis and needs to be managed adequately before LT.[72,73] Diagnostic evaluation of HH must be performed in patients with portal hypertension, presenting with pleural effusion on imaging.[74] Pleural fluid analysis can help rule out complicated hepatic hydrothorax, including the presence of infection or blood.[75,76] An indwelling catheter before LT can prevent rapid volume shifts. SARS-CoV2 infection is common in cirrhosis and needs to be tested before LT, especially in symptomatic patients.[77–79] Computed tomographic scans are suggested before LT in case of a positive polymerase chain reaction test and/or a symptomatic patient.[80]

Key message: Arterial blood gas analysis, chest X-ray, and pulmonary function tests are the minimum tests required before LT.

Infectious Diseases

A complete evaluation, including serological testing for viral hepatitis (Hepatitis A, B, C), human immunodeficiency virus, Epstein Barr virus (EBV), cytomegalovirus (CMV), herpes simplex virus (HSV), venereal disease research laboratory (VDRL), or rapid plasma reagin test (RPR) should be completed. Testing for tuberculosis with interferon-gamma release assay (QuantiFERON Test) is also performed at select centers. In countries with a high incidence of tuberculosis, pretransplant testing for tubercular peritonitis is also suggested with adenosine deaminase testing and TB polymerase chain reaction test.[8] Pretransplant blood, urine, and ascitic fluid cultures are mandatory to rule out infections. Procalcitonin is also performed routinely to identify infection although not considered a gold standard test.[81] Apart from these, a thorough clinical examination of the patient, including skin and soft tissue examination, can identify infection before LT.

Viral diseases can exacerbate liver failure (ACLF) and increase the risk of mortality.[82,83] Vaccination rates in cirrhosis are suboptimal and so is the immune response to vaccination in these immunocompromised patients.[84,85] The Center for Disease Control (CDC) recommends vaccinating all patients with liver cirrhosis.[86] This aids in preparing an individual for LT at the first encounter.

Pretransplant infection increases the risk of posttransplant infection and mortality.[87] Therefore, preventing infections, pretransplant can impact posttransplant outcomes. Statins, beta-blockers, norfloxacin prophylaxis, and albumin infusions have been variably tried across several trials to prevent infections.[82,88–92] However, whether the prevention of infection pretransplant translates to reduced infection risk posttransplant needs to be assessed.

CMV infection is the most common opportunistic posttransplantation infection and affects posttransplant outcomes, morbidity, and mortality. The need for posttransplant prophylaxis is determined by serological testing. Patients with negative serology have the highest risk of CMV infection when transplanted with a CMV-positive organ donor (D+/R-).[93] CMV prophylaxis in post-LT patients has resulted in about an 80% decline in infection in the first 3 months of posttransplantation.[94]

Key message: Active infection is an absolute contraindication; therefore, infection screening is mandatory before LT.

Nutrition and Sarcopenia

Patients with liver disease have numerous factors that contribute to cachexia. Protein-energy malnutrition, sarcopenia, hypoalbuminemia, electrolyte imbalances, and weight loss are common. Loss of appetite commonly occurs due to decreased energy intake due to anorexia, altered taste sensation due to mineral and vitamin deficiencies (magnesium, zinc), unpalatable low-sodium diet, and abdominal distension due to tense ascites.[95] There is also an increase in overall catabolism in the body secondary to increased basal energy expenditure. There is an increase in protein requirements to maintain a positive nitrogen balance. Protein-energy malnutrition has been associated with increased operative risk, morbidity, and mortality. Sarcopenia is prevalent in about 30–70% of patients with cirrhosis. It is associated with higher mortality, increased hospital admissions, poor outcomes post-LT, poor quality of life, and increased risk of complications and morbidity.[96] It is important to identify and optimize sarcopenia prior to transplantation due to these reasons. According to the European Working Group on Sarcopenia in Older People, sarcopenia is defined as low muscle strength, low muscle quantity or quality, and low physical performance. Apart from a simple "eyeball test," that is, visual estimation of a patient's mobility, muscle bulk, and mental approximations of the patient's ability to perform physical exertion imaging studies like computed tomography (CT) (L3 skeletal muscle index), magnetic resonance imaging (MRI), dual-energy X-ray absorptiometry (DEXA), muscle ultrasound, and bioimpedance analysis (BIA) can also be used to assess sarcopenia and nutrition.[97]

The liver frailty index (LFI) is an objective measurement of frailty. It consists of grip strength (measured by

Table 4 Assessment of Sarcopenia.

Test	Method	Reference ranges for sarcopenia
Anthropometric measurements		
Mid-upper arm circumference	Circumference at halfway point between the olecranon process and acromion while arm is bent at 90°	<22.5 cm
Skin-fold thickness	Calliper on posterior aspect of arm, halfway between olecranon process and acromion, measured to the nearest 0.1 mm	Variable dependent on age and sex
Calf circumference	Maximum circumference of calf of lower nondominant leg bent at 90°	<31 cm
Physical performance assessment and muscle strength		
Grip strength	- Dynamometer in dominant hand with base resting in the palm - Maximal isometric effort for 5 s	Men: <27 kg Women: <16 kg
Chair stand	Time needed to rise from seated five times	>15 s for five rises
Timed Get Up-and-Go (TGUG) test	Time needed to rise from seated and walk 3 m away and back with return to seated	≥20 s
Short Physical Performance Battery (SPPB)	- Time to walk 4 m - Feet in a parallel paired position for 10 s - Feet in a parallel nonpaired position for 10 s - Chair stand as above – Each component scored on a scale of 0–4 with 0 equating to test failure and 4 equating to full achievement	
Stair Climb Power Test (SCPT)	- Timed climb of a flight of stairs (4–11 stairs) - Calculated in watts using equation	Age dependent
Liver frailty index	- Grip strength - Timed chair stands - Balance testing	Gender dependent
Skeletal muscle mass index (SMI)	Dividing limb skeletal muscle mass (kg) by square of height (m^2)	Low muscle mass SMI <7.0 kg/m^2 in males, <5.7 kg/m^2 in females

a hand-held dynamometer in the subject's dominant hand); timed chair stands (measured as the time in seconds to do five chair stands with the subject's arms folded across the chest); and balance testing measured as the time in seconds that the subject can balance in three positions (feet placed side-to-side, semi tandem, and tandem) for a maximum of 10 s each.[98] LFI can identify patients with a high risk of wait-list mortality.[99]

Workup also includes subjective global assessment, which has high specificity but low sensitivity for diagnosing malnutrition in alcoholic liver disease.[100] Serological tests such as albumin are frequently used but may not sensitively represent the patient's nutritional status due to its long half-life of 2–3 weeks and frequent exogenous administration pretransplant. Prealbumin has a shorter half-life of 2–3 days and is more sensitive to metabolic status.[101] Other measurements such as anthropometry, hand-grip dynamometry, indirect calorimetry, and BIA help in a complete assessment of nutritional status before LT (Table 4).

Nutrition is individualized for each patient and should be appropriately incorporated into the treatment of patient.[102] Protein intake should not be restricted solely to avoid HE and hyperammonemia.[103] Branched-chain amino acids, high-protein, and high-fiber diet improve muscle mass without causing hyperammonemia or HE.[104] The average amount of protein required to maintain a positive nitrogen balance is about 1.2–1.5 g/kg/day, which improves survival.[105]

Omega 3 fatty acid lipid emulsions have been reported to reduce the incidence of infections and provide adequate calories in patients with advanced liver failure.[106] Moreover, omega-3 fatty acid administration in the perioperative period has been shown to be beneficial in reducing the incidence of infection.[107] However, the role of such prophylactic omega-3 fatty acid administration needs to be assessed in real-world settings for prevention of infection post-LT.

Lastly, the prevalence of obesity among LT candidates has increased, with NAFLD being the fastest-growing indication for LT. Obese patients have an increased risk for portal vein thrombosis and wait-list mortality.[108] A supervised diet and exercise program is the mainstay of treatment. Evidence supporting the use of medications like Liraglutide and Phentermine in decompensated cirrhosis is lacking. Although physicians and surgeons are reluctant to perform elective bariatric surgery in patients with decompensated cirrhosis, a meta-analysis on bariatric surgery in LT reported excellent efficacy of such procedures in this cohort, with comparable weight loss compared to non-LT

setting, but carried a higher rate of morbidity and mortality.[109] Endoscopic procedures for NASH have been shown to be favorable in patients without advanced cirrhosis.[110,111] Further, large RCTs are required to demonstrate the safety and efficacy of bariatric endoscopy in patients with decompensated cirrhosis.

Post-LT, there is a restoration of general health as well as appetite. However, the composition of body fat and muscle may remain suboptimal. Additionally, corticosteroids used for immunosuppression result in weight gain.[112] In a study by Richards *et al.*, LT patients gained about 5 kg in 1 year and 10 kg in 3 years, with about 30% of patients gaining enough weight to be obese.[113] Therefore, dietary management of these patients is crucial in the pre- and post-LT period.

Renal Evaluation

Renal involvement is common in patients with cirrhosis due to functional kidney failure (HRS), intrinsic kidney disease (IgA nephropathy), or the presence of comorbidities that predispose them to chronic kidney disease (CKD).[72] Calcineurin inhibitors are the most commonly used drug post-LT, and renal injury may preclude optimum immunosuppression increasing the risk of graft rejections. Therefore, evaluation of renal function before LT is a must. Complete urine analysis, including examination for red blood cells, proteinuria, and leucocytes, forms the basis of renal function evaluation. Urine protein to creatinine ratio and 24-h urinary protein estimation is also performed to evaluate renal function. Selected patients may require kidney biopsy to establish the diagnosis of CKD and consequently merit simultaneous liver-kidney transplantation. DTPA (Diethylenetriamine pentaacetate) radioactive scan allows the assessment of the kidney's functioning. Patients with diabetes mellitus and hypertension require an ophthalmological examination (for retinopathy) to identify the risk of nephropathy. Ultrasonography of the abdomen for kidney size, doppler studies, and prostate size is a prerequisite for LT.

AKI posttransplant occurs in up to 50% of patients. It is associated with decreased long-term survival and increased rates of acute graft rejection, infections, and length of ICU stay. Several recipients, donor, intraoperative, and postoperative factors predict the development of AKI post-LT.[114] Pretransplant factors associated with posttransplant renal dysfunction include diabetes, hepatitis C, and the presence of HRS. Pre-LT MELD directly correlated with the incidence of post-LT AKI.[115] Hypotension and acute blood loss during surgery (intraoperative factors) are also contributory factors and are more commonly seen in patients with decompensated cirrhosis.[116] Postsurgical complications like sepsis, bleeding, retransplantation with early graft rejection and hypoalbuminemia are associated with post-LT AKI.[116] Post-LT calcineurin inhibitors toxicity, diuretics (for persistent ascites), and prolonged, unnecessary nephrotoxic antibiotics can also lead to AKI. Measures to reduce the incidence of renal dysfunction in postoperative period are required. Terlipressin, a novel vasoconstrictor therapy, is the most extensively used drug for patients with AKI-HRS.[117–119] Terlipressin response before LT reduces the risk of CKD and the need for renal replacement therapy.[120] Perioperative terlipressin has been reported to reduce the incidence of AKI; however, a systematic review and meta-analysis including high-quality studies reported no clinically relevant benefit with perioperative terlipressin therapy.[114]

Hyponatremia

Dilutional hyponatremia in patients with end-stage liver disease has been shown to be a predictor of short-term mortality for patient's on the LT waiting list, irrespective of their MELD score.[121] Numerous studies highlighted a correlation between hyponatremia and preoperative mortality in LT candidates on the wait-list, leading to the addition of serum sodium level into the MELD score.[23,25] Candidates with pretransplant hyponatremia also had higher postoperative morbidity, including longer ICU stay, hospitalization, increased incidence of renal failure, and neurological complications.[122] Serum sodium less than 130 mEq/L generally warrants correction, and measures include fluid restriction, albumin administration, and vaptans.[123–125]

Extrahepatic Malignancy

The presence of pretransplant malignancy (PTM) in LT candidates poses the risk of recurrence of cancer given post-LT immunosuppression. The factors that contribute to these risks include prior malignancy and duration of cancer remission. The timing and candidacy for LT in these patients should be determined by a multidisciplinary team and should include decision-making with detailed staging and treatment information, natural history of cancer recurrence, response to treatment, and favorable disease stage.

AASLD guidelines suggest that in those LT recipients who had a preexisting malignancy, treatment ought to have been curative, and enough time should have passed to rule out recurrence.[69] Depending on the type of malignancy and the documented evidence-based efficacy of treatment, the time period between cancer diagnosis and presumed cure to transplant listing may vary. Every prospective candidate must be up to date on age-appropriate cancer screening tests, such as colonoscopies, mammograms, and Papanicolaou smears.

The recommendations for waiting time interval from the end of cancer treatment to LT listing were made by the International Liver Transplantation Society/Sociedad Española De Trasplante Hepático consensus group. However, these were based on improved recurrence-free

survival with the standard of care treatment in the general population. There are not enough data with respect to LT or sold-organ transplant patients specifically, and it can hypothesized that these recommendations might need modifications based on the increased risk of recurrence in immunosuppressed individuals.[126,127]

No time interval is required after completion of treatment in cancers like superficial nonmelanoma skin cancer, incidental renal tumors with diameter <1 cm, *in situ* breast cancer, superficial bladder cancer, or prostate cancer with Gleason score <6. A 1-year interval is recommended in intermediate-risk breast cancer, low-risk colorectal cancer, high-risk prostate cancer, and melanoma stages IA, IB, IIA. Duration of about 5 years is recommended for high-risk stage IIIC melanomas, high-risk chronic lymphocytic leukemia (CLL) and other lymphomas, high-risk anorectal, colorectal, and gynecological cancers, and high-risk breast cancer.[128]

Psychosocial Evaluation

Transplant surgery is a high-risk and complicated procedure that requires a deep understanding of the risks and benefits and the potential for poor outcomes and the care needed. A complete psychosocial evaluation, including the patient's support system and caregiver assessment, should be completed when a patient is wait-listed. This helps centers identify modifiable factors that may affect transplant outcomes. Lack of insight into the severity of disease and the transplantation procedure poses a huge problem and requires extensive counseling of the patient and their family. The presence of a social support network is essential, and some centers require every patient to have a partner caregiver who is willing to take the responsibility of posttransplant care. This includes accountability in terms of compliance with medications, keeping appointments, and frequent laboratory tests. Biliary complications, seen in up to a quarter of LT recipients, may require surgical or endoscopic intervention, and it is prudent to inform the patient and/or caregiver about this during pre-transplant discussions.[129] Substance use disorders should be addressed prior to transplant, and treatment should be initiated. Unfortunately, many commonly used medical therapies for substance use disorders are not approved for end-stage liver disease.[130] This limits options for patients, but psychotherapy with referral to addiction specialists might be helpful.[131] Most centers require patients to be enrolled in a structured rehabilitation program with a minimum period of sobriety before considering wait-listing a patient.[132] Early transplant for alcohol-associated hepatitis in a select group of motivated patients has been associated with comparable survival to those who undergo LT after 6 months of alcohol abstinence without the risk of significant relapse post-LT.[133] However, several barriers exist, and early LT for AAH continues to be a debatable issue, given the higher healthcare burden.[134]

Miscellaneous Evaluation

Oral health is an ignored aspect of cirrhosis patients. Poor oral health is associated with poorer outcomes in patients with cirrhosis, and dental evaluation is recommended at some centers[135] Patients planned for LT should also be counseled about the financial aspects of LT, especially in India. LT being a major surgery, procurement of blood products, including packed red blood cells, platelets, fresh frozen plasma, and cryoprecipitate, should be made prior to LT. Thorough counseling prior to LT regarding long-term self-care, adherence to medicines, and regular visits post-LT is a must before LT.

DISEASE TRAJECTORY AND PALLIATIVE CARE

The trajectory for patients with decompensated cirrhosis is unpredictable, and the average median survival without transplantation is about 2 years.[136] These patients experience a decline in their functional status, and death might be sudden. The common predictive models used to determine prognosis are Child-Pugh classification and the MELD score. When patients reach end-stage liver disease, the goal shifts toward the quality of life, relief of psychological suffering, and alleviation of physical symptoms. Many wait-listed patients experience severe symptoms and functional decline, so it is important to initiate a discussion around palliation early in the disease course and provide palliative care alongside curative care. The Supportive and Palliative Care Indicators (SPICT) tool can clinically identify patients for palliative care assessment[137] (Table 5).

In the United States, hospice care is limited to patients for whom the expected survival is less than 6 months. When the goal of treatment is not curative, hospice care can be considered. Pain is one of the most prominent symptoms in end-stage liver disease patients. According to the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT) study, patients with ESLD have rates of moderate to severe pain similar to those of patients with lung or colorectal cancer.[138] Other common symptoms include ascites, recurrent variceal bleeding, encephalopathy, pruritus, dyspnea, fatigue and sleep disturbance, psychological symptoms (depression, anxiety), and constitutional symptoms (anorexia, weight loss).

Table 5 Supportive and Palliative Care Indicators Tool.

Liver disease criteria – Supportive and palliative care indicators tool
- Advanced cirrhosis with one or more complications: intractable ascites, hepatic encephalopathy, hepatorenal syndrome, bacterial peritonitis, recurrent variceal bleeds
- Serum albumin <25 g/l, and prothrombin time raised or INR prolonged
- Advanced hepatocellular carcinoma

FUTURE OF LT IN INDIA

India's current pace of development in LT is a significant testament to the procedure's success in the country. India has established itself as South East Asia's regional transplant center, with patients from other nations accounting for roughly a third of all transplant's performed in the country.[5] Training programs are able to churn out transplant surgeons, skilled in both LDLT and DDLT, as multispecialty hospitals establish multidisciplinary teams with allied specialties including critical care, radiology, infectious disease, transfusion medicine, and so on. Around 10–12,000 LT are estimated to be needed in India, and we are far from that goal.[5] To bridge this gap, the number of DDLTs will have to increase. Media, nongovernmental organizations, and the government can work together to achieve this, as was evidenced in the case of the southern state of Tamil Nadu, where deceased organ donation touched 1.3 per million of population, cutting down on commercial transplantation.[139]

In conclusion, patients planned for LT should undergo a thorough evaluation and assessment of each organ's capability to tolerate a major surgery and prevent post-LT complications/morbidity. MELD-Na score for patients with cirrhosis and King's college criteria for ALF remain the gold standard for LT listing.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

IF and VJ prepared the initial draft; AVK critically assessed the manuscript and edited; Tables by IF and RR. All members approved the final draft.

CONFLICTS OF INTEREST

The authors have none to declare.

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