LTSI Consensus Guidelines: Preoperative Cardiac Evaluation in Adult Liver Transplant Recipients

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Cardiovascular disease (CVD) is the leading cause of morbidity and mortality among LT candidates and accounts for up to 40% of the overall mortality within one month. It is influenced by traditional and nontraditional risk factors related to end-stage liver disease. A large proportion of CLD patients have underlying cardiovascular disease (CVD) especially if the etiology is metabolic associated steatohepatitis. Despite the large number of liver transplantations being conducted in India, there is a lack of an evidence-based guidelines for screening of CVD in this patient population. This consensus statement from Liver Transplant Society of India (LTSI) is the first attempt for developing an evidence-based document on preoperative cardiac evaluation from India. A task force consisting of transplant-anesthesiologists, transplant hepatologists, liver transplant surgeon and cardiologists from high volume centres was formed which reviewed the existing evidence and literature and formulated graded

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Abbreviations: ACC: American College of Cardiology; AF: atrial fibrillation; AHA: American Heart Association; AKI: acute kidney injury; aPCC: activated prothrombin complex concentrate; AS: aortic stenosis; AST: American Society of Transplantation; BAV: balloon aortic valvoplasty; BP: blood pressure; BNP: B-type natriuretic peptide; CABG: coronary artery bypass graft; CACS: coronary artery calcium scoring; CAD: coronary artery disease; CI: confidence interval; CCM: cirrhotic cardiomyopathy; CCTA: coronary computed tomographic angiography; CLD: chronic liver disease; CVD: cardiovascular disease; CVE: cardiovascular events; CrCl: creatinine clearance; CT: computed tomography; DAPT: dual antiplatelet therapy; DDLT: deceased donor liver transplant; DDVAP: desmopressin; DES: drug-eluting stents; DM: diabetes mellitus; DSE: dobutamine stress echocardiography; ECG: electrocardiogram; FFP: fresh frozen plasma; FFR: fractional flow reserve; GLS: global longitudinal strain; HCC: hepatocellular carcinoma; ICA: invasive coronary angiography; LMWH: low–molecular weight heparin; LA: long-acting; LAVI: left atrial volume index; LVDD: left ventricular diastolic dysfunction; LTSI: Liver Transplant Society of India; LT: liver transplantation; LVEF: left ventricular ejection fraction; LVH: left ventricular hypertrophy; MASH: Metabolic-dysfunction-associated staetohepatitis; MI: myocardial infarction; MFR: myocardial flow reserve; MPI: myocardial perfusion imaging; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; NT-pro-BNP: N–N-terminal BNP; NPV: negative predictive value; PE: physical examination; PCIs: percutaneous coronary interventions; PCC: prothrombin complex concentrates; ROTEM™: rotational thromboelastogram; SAVR: surgical aortic valve replacement; SPECT: single photon emission computed tomography; TAVR: transcatheter aortic valve replacement; TEG™: thromboelastogram; THR: target heart rate; TIPSS: transjugular intrahepatic portosystemic shunt; TTE: transthoracic echocardiogram; UFH: unfractionated heparin; VHD: valvular heart disease; VKA: vitamin K antagonists; WGs: working groups

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recommendations. The document focuses on identification of underlying cardiac pathologies, risk stratification and optimisation of modifiable cardiac diseases. Implementation of best practices and optimal strategies should be encouraged to improve cardiovascular outcomes in these populations. (J Clin Exp Hepatol 2025;15:102419)

Chronic liver disease (CLD) is a systemic disease that affects multiple organ systems and thus requires careful evaluation of each system before liver transplantation (LT). Older patients with CLD having multiple comorbidities may also be candidates for LT. Metabolic-dysfunction-associated steatohepatitis (MASH)-related CLD is emerging as a common indication globally. A large proportion of these patients could have underlying cardiovascular disease (CVD), which is associated with high morbidity and mortality. Indeed, CVD is the leading cause of morbidity and mortality among LT candidates and accounts for up to 40% of the overall mortality within 30 days.[1–3] Various international societies have reviewed evidence from time to time and proposed guidelines for pre-transplant evaluation of LT recipients.[4,5] Since there are differences in ethnicity, lifestyles, and dietary habits in the Indian subcontinent from the West, it is important to see if cardiac evaluation in an Indian patient requires proceeding differently. In the absence of a robust national deceased donor liver transplant (DDLT) programme in the Indian subcontinent, LT as a treatment is suggested to those who can afford it and often when the options of medical management are exhausted. Besides, in the absence of clear guidelines, every centre that enlists patients for DDLT may not perform a detailed cardiac evaluation at the time of listing. Cardiac evaluation is usually suggested preoperatively once the decision for transplant is made by the family. Living donor LT (LDLT) can be a difficult decision as it involves voluntary donation from a family member and is often considered only when the disease is advanced with multiple episodes of decompensation.

This document aims to review the available evidence, address the existing dilemmas in the current practice of preoperative cardiac evaluation for LT, and form evidence-based guidelines in the context of the Indian population.

METHODOLOGY

In February 2021, the Liver Transplant Society of India (LTSI) executive council formed an expert panel, initially consisting of one senior transplant anesthesiologist, one transplant hepatologist, and one liver transplant surgeon performing high volumes of LT (>200 LTs annually) to formulate guidelines for preoperative cardiac evaluation of LT recipients. This expert panel was expanded to include a total of four senior transplant anesthesiologists, three senior cardiologists, two transplant hepatologists, and one liver transplant surgeon each having more than a decade of experience in evaluating and conducting LTs. Four working groups (WGs) were then created supervised by one senior transplant anesthesiologist of the expert panel (WG lead). 4 to 6 transplant anaesthesiologists were identified from different transplant centres across the country and requested to participate in each WG. The task force thus formed consisted of twenty transplant anaesthesiologists selected from different transplant centres across the country, three senior cardiologists working closely with three high volume LT programmes, two transplant hepatologists and one transplant surgeon from a high volume centre. Each WG focussed on a specific subtopic of cardiac evaluation provided to them. The WG lead coordinated and guided literature search and streamlined the functioning of the group. The WGs reviewed the literature pertaining to their subtopic and held discussions over regular online meetings. The WG performed an extensive literature review using literature searches with PubMed, MEDLINE, and Google Scholar. They also identified areas where there was no available evidence and brainstormed over key areas. Statements and recommendations were circulated and discussed with the WG and expert panel. These were then circulated to all members of the task force. The statements were revised till a consensus of >80% of all members was achieved. The statements were presented and the final consensus was taken during the 5th mid-term LTSI meeting held in November 2023 which was attended by all the experts involved in the guidelines. Subsequently they were written up and amalgamated in the document. The available evidence was classified based on the Grading System for Recommendations (Strength and Quality of evidence)[6] as follows.

Strength of Recommendation

Strong

There is evidence and/or general agreement that a given diagnostic evaluation procedure or treatment is beneficial, useful and effective.

Weak

There is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a diagnostic evaluation, procedure, or treatment.

Quality of Evidence

Level A, Data derived from multiple randomized clinical trials or meta-analyses.
Level B, Data derived from a single randomized trial or nonrandomized studies.

Level C, Only consensus opinion of experts, case studies, or standard-of-care.

CORONARY ARTERY DISEASE

While liver disease was earlier believed to reduce the risk of CAD, it is now well established that CAD is as prevalent in cirrhotic patients as in the general population[7] with a wide reported prevalence ranging between 2.5% and 27%.[8,9] A meta-analysis by Xiao J *et al.* reported that the pooled prevalence of CAD in patients awaiting LT was 15.9% (9.8%–24.7%), and the presence of CAD before LT was associated with higher odds of overall mortality (odds ratio [OR]: 1.4) and cardiac-related mortality (OR: 1.2).[10] In India, the prevalence of CAD and stroke has increased 2.3-fold between 1990 and 2016.[11,12] One report from India by Rohtagi *et al.* stated that the prevalence of CAD is 8.1% (defined as stenosis >50% of a major epicardial coronary artery) in CLD patients.[13] It is important to note that CAD occurs at least a decade earlier in the Indian population than in the Western population. In the large-scale INTERHEART study, it was reported that the median age for myocardial infarction (MI) was 52 years in South Asians as opposed to 62 years in the European population.[14] About half (52%) of deaths due to CVD in India occur before 70 years of age, unlike in the Western population, where only 23% of the deaths reportedly occur before 70 years.[7] Moreover, the study by Gupta *et al.* states that risk factors for CAD increase exponentially in Indians in the fourth decade of life.[15] The estimated prevalence of ischaemic heart disease in India was 23·8 million (95% confidence interval [CI]: 22·6–25·0) in 2016.[12] Thus, given the high prevalence of CAD in India, all adult patients with CLD posted for LT must be screened preoperatively for the presence of underlying CAD (Figure 1).

Risk Factor Assessment

Various risk factors for CAD have been identified in CLD patients. Although the severity of liver disease [indicated by the model for end stage liver disease (MELD) score] does not corroborate with the severity of CAD,[16] Xiao *et al.* identified age, male gender, diabetes mellitus (DM), hypertension, hyperlipidemia, history of smoking, metabolic-dysfunction-associated steatohepatitis (MASH), hepatitis B virus-related CLD and hepatocellular carcinoma (HCC) as risk factors associated with CAD in their meta-analysis.[10] American College of Cardiology (ACC)/American Heart Association (AHA) too has identified DM, prior cardiovascular disease, left ventricular hypertrophy (LVH), age greater than 60 years, smoking, hypertension, and dyslipidaemia as risk factors for CAD in patients with CLD.[4] In addition to these, AHA in their recent guidelines has identified chronic kidney disease, family history of premature CAD, active or past tobacco use and coronary artery calcification score >0 to be risk factors.[17] Plotkin *et al.* reported that the absence of risk factors had a high (≥97%) negative predictive value (NPV) for angiographically significant CAD in cirrhotics.[18] We recommend that patients who are posted for LT with a single risk factor for CAD should undergo further cardiac evaluation.

Recommendations for Risk Factor Stratification

1. *All patients scheduled to undergo LT should undergo a focussed cardiac evaluation with a thorough history and physical examination to screen for risk factors of CAD and other cardiac diseases, followed by resting 12-lead electrocardiogram (ECG) and 2D echocardiography (strong/level C)*
2. *We recommend that patients with any one of the following risk factors: Age ≥40 years, hypercholesterolemia, hypertension, smoking/tobacco use, prior cardiovascular disease, DM, left ventricular hypertrophy, or MASH should undergo further cardiac evaluation (strong/level B).*
3. *We recommend that patients with no risk factor should be considered at low risk for CAD and can proceed for LT after ECG and echocardiogram (strong/level B).*

Modalities of Cardiac Evaluation

Cirrhotic patients often have poor exercise tolerance, limiting the utility of tests like the 6-min walk test and treadmill test. Thus, pharmacologic stress tests or computed tomography (CT)-based tests like coronary artery calcium scores (CACS) are frequently performed to rule out CAD.

i) **Dobutamine stress echocardiography (DSE):** Although DSE is a cardiac stress test commonly advised to patients awaiting LT, it is perhaps not very useful for diagnosing CAD in CLD patients. Since patients with CLD have hyperdynamic circulation and hypercontractile ventricles, adjacent ventricular areas get tethered to each other under stress making the detection of small ischaemic changes difficult. Moreover, this patient population has chronotropic incompetence and with frequent use of beta-blocker therapy for management of variceal bleeding, they may not achieve target heart rate (THR) during stress test. Several studies have consistently demonstrated that DSE has a poor predictive value for CAD in CLD patients.[19–21] In a recent study, Kutkut *et al.* reported that the stress echocardiography had a low sensitivity of 37% in detecting significant CAD.[22] Thus stress echocardiography is not a good screening test for detection of CAD. Bonou *et al.* reported that the NPV of DSE ranges between 48% and 100%.[23] However, Doytchinova *et al.*[24] concluded that after a large-scale study that patients with a positive DSE are prone to a higher incidence of cardiovascular events (CVE) following transplantation, despite its low sensitivity.

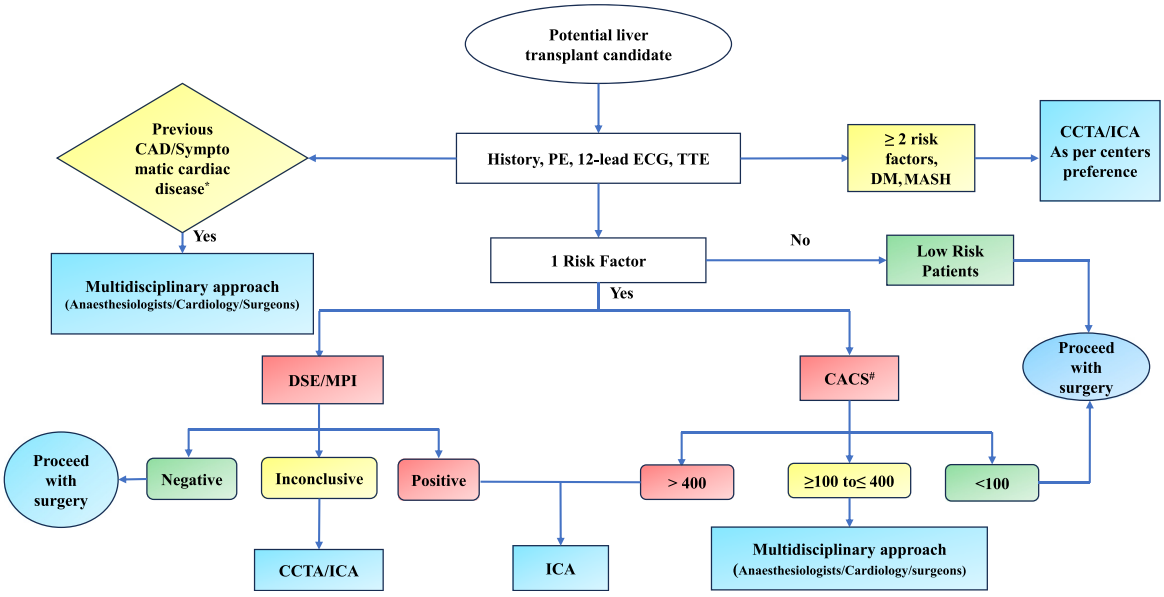

Figure 1 The - approach for coronary artery disease evaluation and risk stratification in potential liver transplant candidates.
Figure legends:*Previous coronary artery disease (CAD) is defined as a history of MI or revascularization (coronary artery bypass grafting or percutaneous coronary intervention) or >50% stenosis in a major coronary artery. Symptomatic cardiac disease is defined as a history of angina, angina equivalent, arrhythmias, or any symptoms suggestive of congestive heart failure. #Risk factors for CAD are: Age ≥40 years, hypercholesterolemia, hypertension, smoking/tobacco use, prior cardiovascular disease, left ventricular hypertrophy, DM, and MASH. @ CACS: CACS is preferable to NIST in centres where it is available. CAD: coronary artery disease; PE: physical examination; ECG: electrocardiogram; TTE: transthoracic echocardiogram; MASH: metabolic-dysfunction-associated steatohepatitis; DM: diabetes mellitus; CACS: coronary artery calcium scoring; CCTA: coronary computed tomographic angiography; DSE: dobutamine stress echo; MPI: myocardial perfusion imaging; ICA: invasive coronary angiography.

ii) **Single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI):** MPI using a pharmacologic vasodilator (dipyridamole, adenosine, or regadenoson) does not depend on achieving a THR. However, as these agents work by inducing vasodilation in non-ischaemic territories, the pre-existing vasodilatory state associated with CLD may influence the results.[21] Like DSE, SPECT imaging also has a low sensitivity as an initial screening test in CLD patients.[25] In a large-scale study of 2500 patients, Duvall *et al.* reported that abnormal stress test was seen in only 7.8% of LT patients as compared with 34.3% in the general population highlighting the pitfalls of using stress test in CLD patients.[26] However, the utility of SPECT to predict post-LT CVE increased considerably (sensitivity of 80% and specificity of 94%) in the presence of risk factors of CAD.[27]

Only a few studies have directly compared DSE and SPECT MPI for screening CLD patients for CAD. Snipelisky *et al.* reported that both modalities had equal efficacy.[28] In contrast, Soldera *et al.*, in a meta-analysis, reported that both DSE and MPI had low sensitivities in detecting CAD.[29] Hence, SPECT MPI or DSE are not ideal tests to diagnose CAD in CLD patients and patients with no risk factors may not benefit further from these investigations.

iii) **Computerised tomography (CT)-based evaluation:** CT-based tests are advantageous as they neither depend on the patient's ability to achieve a THR nor are they influenced by the pre-existing vasodilatory state. CT-based tests include coronary artery calcium scores (CACS) and coronary CT angiography (CCTA).

iii **a) Coronary artery calcium scores:** CACS is gaining popularity as a valuable tool for evaluating CAD in the general population. It is a well validated measure for the presence of subclinical atherosclerosis.[30] Patients with higher atherosclerotic cardiovascular risk factors have higher CACS than patients without risk factors.[31] It is a stronger predictor of cardiac risk than other serum biomarkers.[32] While older guidelines do not incorporate CT-based testing in their algorithm, recent evidence is available for CACS and CCTA to detect CAD in LT recipients.[33,34] A CACS ≥400 is associated with angiographically significant CAD in patients posted for LT, with one study reporting that 24% of patients required revascularization.[35,36] CACS >400 has been associated with a higher incidence of postoperative CVE 1 and 4 months after LT.[35,36] In a study by West *et al.*, a threshold

CACS of 251 maximised the sensitivity and specificity for detecting obstructive CAD.[37] Based on the current evidence, we recommend that CACS may be considered for preoperative evaluation in place of MPI/DSE in patients with one risk factor for CAD.

iii **b) Coronary computed tomography angiography (CCTA):** Most data on CCTA has been derived from the general population where CCTA has been found to be a viable alternative to invasive coronary angiography (ICA) in excluding obstructive CAD with an NPV of >95%.[38,39] While the data on LT candidates is limited, in a large retrospective study of 2118 patients, Moon *et al.* reported that CCTA had a high NPV of 97.5% in ruling out MI following LT.[40] The utility of CCTA in ruling out significant CAD has been corroborated by other studies.[41,42] CCTA images are limited by diffuse coronary calcifications and has the potential to cause contrast-related allergy and nephrotoxicity. However, unlike conventional angiography, the risk of acute kidney injury (AKI) is lower in CCTA and may thus be preferred in patients with pre-existing renal dysfunction.[43,44] Computed tomography (CT)-derived fractional flow reserve (FFR) provides additional information on coronary blood flow and its utility is being explored.[45] We recommend that CCTA be performed in all patients with inconclusive stress tests and may be considered in patients with a CACS of 100–400. If feasible, FFR is a valuable additive to CCTA and should be used with every scan to improve diagnostic performance. CCTA may be considered an alternative to ICA when ICA is relatively contraindicated. Considering the limitation of CCTA in patients with previous coronary stents, patients with CAD should be evaluated using a multidisciplinary approach involving a cardiologist.

iv) **Invasive coronary angiography (ICA):** ICA remains the gold standard for detecting and managing CAD through percutaneous coronary interventions (PCIs). Although factors like coagulopathy and AKI which are often associated with CLD may be a matter of concern during ICA, recent evidence suggests that ICA can be safely performed in this subset of patients, even if done on an emergency basis.[46] The use of ICA is preferred over other cardiac tests in a few centres.[17] Though it is an invasive procedure, ICA has high accuracy to detect obstructive CAD compared with other modalities. Thus, it should be performed in patients when other tests are positive or inconclusive. The need for an ICA in patients with previous CAD or coronary artery bypass graft (CABG) should be decided in consultation with a cardiologist. A radial rather than femoral approach may reduce bleeding complications in patients with CLD. Percutaneous therapeutic options for CLD patients should take into account the increased risk of bleeding with dual antiplatelet therapy (DAPT). Options for percutaneous coronary interventions may include bare metallic implants or newer stents, which need a shorter duration of DAPT.[21] The role of revascularisation in asymptomatic patients is still not well established. Studies on the effect of revascularisation on the long-term survival of LT recipients have led to conflicting results, and more research is required to understand its definitive impact.[47]

Positron emission tomography myocardial perfusion imaging (PET MPI) is a relatively newer modality to detect CAD with the ability to determine myocardial flow reserve (MFR). In non-cirrhotic populations, it has been shown to have 90% sensitivity for detecting significant coronary obstruction (>50% stenosis) which is higher than that of CCTA.[1,2] Recent evidence has shown that reduced global MFR ≤1.38 and reduced resting left ventricular ejection fraction on a PET MPI was associated with a higher risk of major adverse cardiac event (MACE) following LT.[3] Tincopa *et al.* compared DSE and PET MPI in LT candidates and found that PET/CT MPI may be preferred to DSE in older patients and those with known cardiovascular disease.[48] However, further studies are required to determine its sensitivity to detect significant CAD in the vasodilatory state of cirrhosis. PET MPI remains a promising modality for detecting CAD and may be considered if available.

Approach to a patient with Risk Factors

There is no uniform consensus regarding the number of risk factors at which patients should undergo detailed cardiac evaluation. The American Association for the Study of Liver Diseases in 2013 recommended that all LT candidates should undergo stress echocardiography as the initial screening test.[3] ACC/AHA guidelines recommend all LT candidates with three or more traditional risk factors to undergo cardiac evaluation using noninvasive stress testing regardless of exercise tolerance as the presence of three or more risk factors provides high predictive accuracy in detecting obstructive CAD in cirrhotics.[4,49] While the American Society of Transplantation (AST) recommends that patients with two or more traditional risk factors for CAD or DM should be evaluated further.[5]

In cirrhotic patients, there is now enough evidence to suggest that DM and MASH are independently associated with a higher risk of obstructive CAD. DM is an independent risk factor for the occurrence of obstructive CAD, even when adjusted for other risk factors.[50] The estimated prevalence of DM in patients with cirrhosis is around 30%.[51,52] Diabetics also have a significant association with other atherogenic risk factors than nondiabetic

patients, like coexisting hypertension, obesity, hypertriglyceridemia, and non-alcoholic fatty liver disease (NAFLD). Several studies suggest that type 2 DM may have an etiological role in CLD and HCC.[53,54] In cross-sectional retrospective studies conducted on cirrhotic patients, the presence of DM was associated with an increased risk of complications regardless of aetiology.[55] According to the Verona diabetes study conducted in patients with type 2 DM and CLD which included more than 7000 individuals, the 5-year mortality was 2.52-fold greater (CI: 1.96–3.2) than in the general population.[56] The AST has also acknowledged that the presence of DM alone is sufficient to warrant further noninvasive cardiac imaging.[57]

MASH is associated with an enhanced risk for CAD, independent of other metabolic risk factors.[57] It is associated with subclinical myocardial dysfunction, symptomatic diastolic dysfunction, and increased left atrial volume, which is a robust predictor of morbidity and mortality in Heart Failure (HF). In addition, the presence of MASH has often been associated with critical coronary stenosis.[23,58] Stine *et al.* suggested that patients classified as high-risk MASH (i.e. patients fulfilling the following criteria: age >60 years, body mass index >30 kg/m^2, hypertension, and DM) should undergo coronary angiography though this suggestion is not based on actual data.[37] G Targher *et al.* showed that the risk of fatal CVEs was significantly higher in NAFLD than in non-NAFLD patients.[59] Given the extensive evidence, the authors consider MASH an independent risk factor for CAD.

Recommendations

4. *We recommend that patients with one risk factor, should undergo non-invasive stress testing (NIST) or CACS as per centre preference/experience (strong, level B)*
5. *Among modalities of NIST, no recommendation can be made for preferring one modality of NIST over the other (strong, level B).*
6. *CACS may be preferable over NIST in centres where it is available (weak, level C)*
7. *ICA should be performed in all patients when either the stress test is positive or when CACS > 400 (strong, level B)*
8. *If CACS <100 or NIST is negative then patients should proceed for surgery without further testing (strong/level B).*
9. *In patients with a CACS ≥100 to ≤400, a multidisciplinary approach should be used to evaluate further evidence (weak, level C).*
10. *CCTA maybe considered in patients with a CACS of 100–400 (weak, level C).*
11. *CCTA or ICA should be performed in patients to rule out CAD when noninvasive stress tests are inconclusive (strong, level B)*
12. *We recommend that patients with two or more risk factors or MASH or DM should undergo a computed tomography coronary angiography/ICA as the risk of obstructive CAD is high (strong/level C).*
13. *CCTA maybe considered as an alternative to ICA when ICA is relatively contraindicated (weak, level C).*
14. *If CCTA is suggestive of CAD, ICA should be performed (strong, level B)*
15. *CCTA may be considered in situations where ICA may be relatively contraindicated (weak, level C)*

CIRRHOTIC CARDIOMYOPATHY AND ITS ASSESSMENT

Cirrhotic cardiomyopathy (CCM) is characterised by structural and functional changes in the heart in the absence of primary cardiac disease and is associated with an impaired response to stress. It is estimated that 40–50% of patients with CLD have CCM[60] with majority of patients being asymptomatic under normal conditions. Periods of stress like LT surgery, transjugular intrahepatic portosystemic shunt (TIPSS), exercise, and infections may unmask cardiac dysfunction and precipitate cardiac failure.[61–63] The initial 2005 Montreal World Congress of Gastroenterology definition of CCM was based on echocardiographic and biochemical criteria. Since then, the definitions of systolic and diastolic dysfunction have been modified by the American Society of Echocardiography and the European Association of Cardiovascular Imaging to include tissue Doppler and strain patterns.[64] In keeping with this, the Cirrhotic Cardiomyopathy Consortium redefined CCM in 2020 as systolic dysfunction is characterised by either left ventricular ejection fraction (LVEF) <50% or absolute global longitudinal strain (GLS) <18%; diastolic dysfunction is said to be present if three or more of the following are present. These include a septal e′ velocity <7 cm/s, E/e′ ratio >15, left atrial volume index (LAVI) >34 ml/m^2, or tricuspid regurgitation (TR) jet velocity >2.8 m/s in the absence of POPH (Table 1).[65] For patients who meet 3 or more of the diastolic dysfunction criteria, the grade of diastolic function (I vs II vs III) can be determined based on the E/A ratio. Future research areas have been identified, including abnormal chronotropic or inotropic response, electrocardiographic abnormality, electromechanical uncoupling, myocardial mass change, serum biomarkers, and chamber enlargement. Screening patients for CCM before LT is important as perioperative stress may precipitate myocardial dysfunction, resulting in clinical HF. However, detection of CCM is often challenging as signs and symptoms typically attributed to overt HF (dyspnoea, pedal oedema, ascites) are often seen in decompensated cirrhotic patients. Hence, detection of HF and its progress to higher stages (C or D) requires a comprehensive cardiovascular evaluation which needs to be repeated at regular intervals to monitor the progression of HF.

Table 1 Cardiomyopathy Consortium Redefined CCM in 2020.

- Systolic dysfunction: either one of the following
  - Left ventricular ejection fraction (LVEF) < 50%
  - Absolute global longitudinal strain (GLS) < 18%;
- Diastolic dysfunction: Presence of three or more of the following:
  - Septal mitral annular early diastolic velocity (e′) by tissue Doppler <7 cm/s o mitral inflow early diastolic velocity (E) to e′ ratio >15
  - Left atrial volume index (LAVI) > 34 ml/m^2
  - Tricuspid regurgitation (TR) velocity >2.8 m/s in the absence of POPH
- Future areas of research
  - Abnormal chronotropic or inotropic response o electrocardiographic abnormality
  - Electromechanical uncoupling
  - Myocardial mass change
  - Serum biomarkers
  - Chamber enlargement
  - Cardiac magnetic resonance imaging

CCM: cirrhotic cardiomyopathy

Assessment of Left Ventricular Systolic Function

The reduced afterload seen in CLD patients results in normal or increased LVEF, limiting its utility as a measure of systolic function. In addition, many patients are treated with beta-blockers which make stress testing unreliable. However, cardiovascular imaging like strain imaging using echocardiography can identify contractile dysfunction by evaluating circumferential, longitudinal, radial and transverse strain. Of these, GLS is an important parameter in identifying left ventricular (LV) dysfunction in the general population.[66] GLS is an earlier marker of contractile dysfunction than LVEF. Though measured in negative values, absolute values are reported to avoid confusion. GLS values >18% (more negative) are normal, GLS less than 16% is abnormal, and GLS 16–18% is considered borderline in adults.[67] Post-LT mortality is high in patients with LVEF< 50% and most centres would restrict LT to patients with LVEF >40%.[5] In a retrospective analysis, Kwon *et al.* found that in patients with a MELD ≥20, LVEF ≤60% was strongly associated with higher post-LT mortality rates.[68]

Assessment of LV Diastolic Function

Diastolic dysfunction has an important association with development of post-transplant HF.[69] Assessing diastolic dysfunction is more complex and a single parameter cannot be used to identify LV diastolic dysfunction (LVDD).[70] Pulsed wave doppler on 2D echocardiography is used to measure early peak diastolic filling velocity (E), late peak diastolic filling velocity (A), and the E/A ratio. E/A ratio of <0.8 indicates diastolic dysfunction. However, E/A ratio is affected by pseudonormalisation. Current recommendations suggest the use of tissue doppler, strain patterns, and TR jet velocity. Tissue doppler is not dependent upon cardiac load and does not exhibit pseudonormalisation. It is performed by placing the sample volume at the mitral annulus. The early peak diastolic mitral annular velocity (e′) is measured. The CCM consortium suggests that medial velocity should be reported for the sake of convenience and its value < 7 cm/s is a marker of diastolic dysfunction. The E/e′ ratio is then used to further classify LVDD into 4 stages. Decreased e′ velocity and a decreased E/A also occur physiologically due to ageing. Increased LAVI is an established parameter in diagnosing diastolic dysfunction.[70] However, it should be interpreted with caution as the chronic hyperdynamic state seen in CLD patients leads to enlargement of cardiac chambers even in the absence of diastolic dysfunction. As with LAVI, tricuspid regurgitation (TR) can also be seen in CLD patients in the absence of diastolic function when there is associated porto-pulmonary hypertension (PoPH). Thus, the CCM consortium recommends that TR velocities should be used for the diagnosis of CCM in the absence of PoPH.[66] Diastolic dysfunction is a risk factor for allograft rejection, graft failure, and mortality.[71,72] It is also been reported that pre-transplant elevation of E/e′ increased left atrial volume index and lower mean arterial pressure (P = 0.03) were independent predictive factors of heart failure after transplant.[69]

Other Parameters

The limitations of stress tests in CLD patients have been described in the previous section. The utility of ECG to diagnose CCM is also limited. Prolonged heart rate-corrected QT interval (QTc) on ECG is a common abnormality seen among patients with CCM. However, it is nonspecific and is reported to be present in up to 50% of CLD patients. Similarly, LV enlargement may be seen in CLD patients due to a high-output cardiac state. Cardiac magnetic resonance imaging is being explored for its ability to determine myocardial inflammation, fibrosis, and myocardial extracellular volume and has shown promising results.[73] Three-dimensional echocardiography and strain/strain-rate analysis using speckle tracking echocardiography are being increasingly used nowadays to assess long-acting (LA) phasic function.[74] The utility of biomarkers of cardiac dysfunction like B-type natriuretic peptide (BNP), N –N-terminal BNP (NT-pro-BNP) and cardiac troponins are well described for non-cirrhotic populations.[75] In cirrhotic patients, abnormal levels of cardiac biomarkers are often associated with worsening CLD and portal hypertension.[76,77] In patients with CCM, BNP and NT-pro-BNP have been associated with HF though more evidence is required in this area to recommend their use.[78]

Recommendations

16. *We recommend that all LT candidates should undergo comprehensive cardiac echocardiography incorporating tissue doppler imaging and strain imaging (strong, level B)*
17. *We recommend to follow the 2020 Cirrhotic Cardiomyopathy Consortium definition of CCM (strong, level B)*
18. *We suggest that cardiac imaging may be repeated at 6-month intervals in patients diagnosed with CCM to detect the progression of the disease (weak, level C)*

VALVULAR HEART DISEASE

Valvular heart disease (VHD) is relatively common among the Indian population but the reported literature on outcomes in patients with symptomatic and asymptomatic severe VHD undergoing LT is lacking. Rheumatic heart disease is fairly common with an estimated prevalence of 500–750 per one lakh Indian population. While rheumatic mitral stenosis is the commonest valvular lesion observed,[79,80] calcific aortic and degenerative mitral valve disease is seen in 250–500 per one lakh population.[81]

The perioperative outcome of LT depends upon the type and severity of associated valvular lesions.[82,83] All CLD patients scheduled for LT should undergo clinical and echocardiographic evaluation to screen for underlying VHD. Severity of VHD should be graded based on ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease.[49]

Stenotic lesions tend to produce more haemodynamic alterations than regurgitant lesions. Haemodynamic changes are especially pronounced during the anhepatic stage, during inferior vena cava cross-clamping and post-reperfusion stage.

Stenotic Valvular Lesions

Mild to moderate stenotic VHD is usually reasonably well tolerated in the perioperative period.[82] Though both aortic and mitral stenotic and regurgitant lesions are encountered in cirrhotic patients, the availability of literature for coexisting aortic stenosis (AS) is higher. During non-cardiac surgery among cirrhotic patients, severe AS increases mortality by 10% and perioperative complications by 31%.[83] On echocardiography, the severity of flow gradients may be overestimated due to the pre-existing high cardiac output state of CLD.[84] Hence, during the preoperative evaluation of stenotic VHDs, flow-independent parameters (e.g. valve area) should also be considered for assessing the severity of the disease.[85] The estimated prevalence of severe AS, defined by a valve area <1 cm^2, reported among cirrhotic patients is 2–5%.[86] In addition, coronary evaluation for the concomitant presence of CAD in patients with symptomatic severe AS should be considered.[87] Symptomatic patients with severe AS should be optimised prior to LT. Balloon aortic valvoplasty (BAV) has been reported as a bridge to LT; however, current evidence suggests that BAV leads to an increase in morbidity and mortality (due to associated post-procedure severe aortic regurgitation and stroke) and thus other modalities like transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR) for treatment of severe AS are preferred.[88] TAVR is currently preferred to SAVR in high-risk patients with severe stenosis when feasible. TAVR avoids the need for cardiopulmonary bypass and major surgery. Thus, TAVR theoretically offers more advantages in cirrhotic patients than with SAVR. Though clinical trials comparing the two modalities in cirrhotic patients are lacking, the current literature based on case series and case reports suggest that TAVR may be safer than SAVR.[83,89–91] However, it is important to note that a multidisciplinary approach to choose the modality of treatment of AS is necessary as SAVR is favoured in certain patients like those with severe calcification of a bicuspid valve. Other factors like history of myocardial infarction, stroke, hypertrophic obstructive cardiomyopathy, ejection fraction <20%, etc are also taken into consideration while choosing the modality of treatment. In addition, in select patients combined aortic valve surgery and liver transplantation has been performed successfully. However, in light of the sparse data, surgical expertise and centre preference currently defines the preference for combined surgery or sequential surgeries.[92–94] Valvotomy or valve replacement should be considered in patients with severe mitral stenosis (MS) and symptomatic moderate MS with secondary severe pulmonary artery hypertension. Gasperi *et al.* reported a case of simultaneous LT and mitral valve replacement in a patient of hepatitis C who unfortunately passed away on post-operative day 51 highlighting the risk of surgical valve replacement in cirrhosis.[95]

Regurgitant Valvular Lesions

Functional regurgitant lesions involving mitral, tricuspid, and aortic valves are commonly seen in CLD patients and are usually mild to moderate in severity and are managed medically.[96] The reported prevalence of regurgitant lesions involving mitral or tricuspid valves in LT recipients is approximately 28%. In contrast, only 0.65% of cirrhotic patients reported to have moderate to severe aortic regurgitation.[97] An increase in the severity of tricuspid regurgitation could represent either fluid overload or porto-pulmonary hypertension. Patients with regurgitant valvular lesions with elevated pulmonary artery pressures (>35 mmHg) should be evaluated as per LTSI consensus guidelines for preoperative pulmonary evaluation to rule out underlying porto-pulmonary hypertension (POPH).[98]

The low systemic vascular resistance (SVR) seen with regurgitant lesions can get worse with underlying CLD. Though some reports suggest that patients with regurgitant lesions have successfully undergone LT, data on the effect of regurgitant lesions on post-LT outcomes is conflicting.[97,99] Severe structural regurgitant lesions with associated reduced LVEF require valvular intervention, and a multidisciplinary decision should be made to optimise the patient before LT.[49] In a retrospective analysis on cirrhotic patients with significant mitral regurgitation who underwent either transcatheter edge-to-edge repair (TEER) or surgical replacement, Sawalha *et al.* found that the in-hospital mortality was lower in patients with TEER.[100] Patients who have undergone previous surgical correction of VHD and have a prosthetic valve can undergo LT after evaluation of valvular function. Preoperative TTE can be used for screening of infective endocarditis. Given its higher sensitivity, transoesophageal echocardiography is recommended in patients with high suspicion of infective endocarditis (IE) with an inconclusive TTE.[101] Two or more blood culture samples (more than 6 h apart) should be obtained in patients suspected to have IE in patients with VHD for the diagnosis of IE.[49]

Recommendations

19. *We recommend all CLD patients scheduled for LT undergo clinical and echocardiographic evaluation to screen for underlying VHD (strong/level C).*
20. *Mild to moderate VHDs are usually well tolerated in the perioperative period and are not a contraindication to LT. Patients with severe structural valvular heart disease should undergo surgical or percutaneous valvular interventions before LT. A multidisciplinary approach should be adopted to optimise these patients (strong/level C).*
21. *We recommend coronary evaluation for concomitant CAD in patients with symptomatic severe aortic stenosis (weak/level C)*

HYPERTENSION

The prevalence of arterial hypertension in patients with cirrhosis is about 3%–7% compared with 10–15% in the general population.[102] The lower incidence is attributed to the vasodilatory state due to low SVR.[103] The prevalence of hypertension in patients with NAFLD is about 45% and is higher compared with other etiologies of cirrhosis.[104] ECG and echocardiographic studies in hypertensive patients could reveal left axis deviation and LVH, respectively. Patients with hypertension are at high risk of cardiovascular disease (CAD), stroke, and chronic renal disease. Hypertension is one of the modifiable risk factors for adverse cardiovascular events in patients undergoing LT. Preoperative optimisation of hypertension is necessary to reduce perioperative hemodynamic adverse events. In the absence of studies on the optimal blood pressure (BP) target in cirrhotic patients, guidelines developed for the general population should also be applied to this subset of patients. BP <140/90 mm of Hg is a reasonable target with the use of antihypertensive medication.[105,106] Beta-blockers like carvedilol offer a dual advantage of decreasing portal hypertension along with management of systemic hypertension.

Recommendation

22. *We suggest attaining a target BP < 140/90 mm of Hg while optimising antihypertensive medication in cirrhotic patients (weak, level C)*

PERICARDIAL DISEASES

Pericardial effusion typically occurs in patients with advanced cirrhosis due to fluid retention, hypoalbuminemia, renal failure, and coexisting cirrhotic cardiomyopathy. Other potential causes are due to multiple systemic disorders such as tuberculosis, neoplasms involving the pericardium, and collagen vascular disorders.[107] Significant pericardial effusion leads to low hepatic blood flow by reducing cardiac output and promotes hepatic congestion by augmenting right heart pressures. Patients with cirrhosis generally have a subacute presentation, and often, the diagnosis is made incidentally on routine echocardiography. Asymptomatic patients with minimal effusions do not require any intervention. Patients with a pericardial effusion who are hemodynamically unstable with evidence of right heart dysfunction or cardiac tamponade in echocardiography require immediate pericardiocentesis.

Recommendation

23. *We recommend that asymptomatic patients with minimal effusions should not undergo any intervention. TTE-guided pericardiocentesis is reserved for pericardial tamponade or significant effusions impairing the functions of the right heart (strong, level C)*

Arrhythmias

Patients with CLD are predisposed for the development of arrhythmia. The plausible causative factors include impaired autonomic function, metabolic and electrolyte imbalances, and underlying CCM.[108] Atrial fibrillation (AF) is a common arrhythmia with a prevalence of 5.4% in patients with CLD.[109] The incidence of AF following LT is reported to be as high as 8.5%.[110] Patients with NAFLD and associated hypercholesterolemia, and DM are considered high-risk factors for the development of cardiac arrhythmia.[111,112] Patients with hepatic cirrhosis and concomitant AF have an increased risk of in-hospital

mortality, stroke, AKI, and major cardiovascular events[113] Patients with chronic AF may receive oral anticoagulants. Oral anticoagulant drugs should be stopped prior to LT and bridging therapy with unfractionated heparin (UFH) or low–molecular weight heparin (LMWH) should be initiated for prevention of thromboembolic complications. Another common electrophysiological abnormality reported in CLD patients is prolonged QT_c interval (>450 ms in males and >470 ms in females). Prolonged QT interval is seen in 30%–70 % of patients with CLD.[63,114] However, Cesari *et al.* in their retrospective study found no association of prolonged QT_c in CLD patients with pre-existing CLD.[115]

In patients with QT prolongation, drugs known to prolong QT should be avoided due to the risk of precipitating polymorphic ventricular tachycardia.

Recommendations

24. *We recommend that all patients with pre-existing AF should undergo transthoracic ECHO to search for structural cardiac abnormalities and the presence of a thrombus. (strong, level B).*
25. *For CLD patients with chronic AF receiving oral anticoagulation therapy, we recommend stopping oral anticoagulants and initiating bridging therapy with UFH/LMWH (strong, level C).*

Clinical Practice Guidelines

SPECIAL CONSIDERATIONS

Patients on Direct Oral Anticoagulants

Cirrhotic patients are in a state of unbalanced hemostasis, making them vulnerable to bleeding as well as thrombosis. Patients with Budd Chiari syndrome and portal vein thrombosis receive anticoagulation therapy. Patients with chronic atrial fibrillation (AF) or having mechanical heart valves are another group of patients who may receive anticoagulant therapy. Direct oral anticoagulants (DOACs) include vitamin K antagonists (VKAs) like warfarin and acenocoumarol, direct thrombin inhibitors like dabigatran and factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban). All drugs can be safely used for patients having Child–Pugh class A cirrhosis. As per drug regulatory authorities, VKA, dabigatran, and apixaban may be used with caution in patients with Child–Pugh class B cirrhosis while rivaroxaban and edoxaban are contraindicated. Direct thrombin inhibitors and factor Xa inhibitors are contraindicated in patients with Child–Pugh class C cirrhosis.[116] There is a lack of literature on the preoperative management of anticoagulants, and antiplatelets in cirrhotic patients and management strategies are largely defined using guidelines from the general population.[117] (Table 2). Routine coagulation monitoring is not needed in patients receiving DOAC. Monitoring might be necessary for patients with impaired renal function (creatinine clearance <30 ml/min), very low body weight, and advanced geriatric age. Analysis of anti-Xa and anti-IIa levels suffer from relatively high costs and long turnaround times. Specific viscoelastic assays such as Rotational thromboelastogram (ROTEM™) (low Tissue Factor, Thrombin b), Thromboelastogram (TEG™) (activated factor Xa, Direct thrombin inhibitors), and Clotpro™ (RVV, ECA) can be used to provide point-of-care (POC) information regarding DOAC activity.[118] LT is associated with a high risk of intraoperative haemorrhage and thus DOACs should be stopped before LT. The duration for which DOACs should be stopped depends upon the drug being used (Table 2). Bridging therapy with low–molecular weight heparins (LMWH) should be initiated to prevent thrombotic complications. The routine use of blood products for the reversal of anticoagulation is not recommended except in emergency settings and patients undergoing cadaveric transplants.[119]

Patients with DAPT

Antiplatelet drugs are commonly prescribed in patients with arterial thrombosis like CAD and cerebrovascular diseases. Antiplatelet therapy includes aspirin, P2Y12 receptor blockade (clopidogrel, prasugrel, and ticagrelor), and glycoprotein receptor IIb/IIIa inhibitors (abciximab, tirofiban, and eptifibatide). DAPT is a combination of aspirin with another antiplatelet drug of a different class which is commonly a P2Y12 receptor blocker like clopidogrel or ticagrelor. Cirrhotic patients may be already receiving DAPT if they are suffering from CAD and have undergone PCI. Management of patients receiving DAPT relies on balancing the risk of intraoperative bleeding and the risk of perioperative stent thrombosis. There is a lot of heterogeneity in the management of patients on DAPT undergoing LT. LT has been safely conducted in patients after stopping DAPT. Newer generations of drug-eluting stents (DES) have a reduced risk of stent thrombosis and a shorter course of 1 month of DAPTs can be used in patients at high risk of bleeding.[120] Koshy *et al.* recently reported that CLD patients with second-generation DES underwent LT successfully with aspirin monotherapy alone after receiving a brief course of DAPT for 1–3 months with no increase in perioperative MACE.[121] In a similar context, Saarcco *et al.* also reported that LT was safely conducted on patients receiving aspirin monotherapy. In their cohort, patients received DAPT for 31–40 days after stenting, and LT was performed with a median duration of 77 days (12–172 days) after discontinuation of DAPT.[122] We consider that in patients listed for LT and having newer-generation DES, a short course of DAPT of 30 days is considered appropriate after which patients can undergo LT with aspirin monotherapy alone. A multidisciplinary decision involving cardiology is necessary for optimising DAPT therapy to balance the risk of surgical bleeding with stent thrombosis. Correction of platelet dysfunction

Table 2 Management of Anticoagulant/Antiplatelet Drugs During the Perioperative Period of Liver Transplantation.

Drug	Mechanism	Half life	Cessation before LT	Restart after LT	Emergency reversal	Notes
Warfarin	Vitamin K antagonist	40 h	5 days	1–2 days	PCC, FFP, Vit K	Bridging in specific cases
Dabigatran	Direct thrombin inhibitor	14 h	CrCl>50 ml/min —3 days CrCl<50 ml/min —4 days	1–2 days	aPCC, idarucizumab, cryoprecipitate	Avoid when CrCl <15 ml/min
Apixaban	Factor Xa inhibitor	7–8 h	2 days		Four factor PCC	
Rivaroxaban		8–9 h			Andexanet alfa, aPCC	
Edoxaban		8–10 h				
Aspirin	COX-2 irreversible inhibitor	7–10 days	Usually continued	Usually continued	2–3 apheresis platelets DDAVP	Cangrelor—intravenous P2Y12 reversible inhibitor with $t_{1/2}$ 3–6 min
Clopidogrel	P2Y12 irreversible inhibitor	7–10 days	5 days	1–2 days		
Ticagrelor	P2Y12 reversible inhibitor	5–7 days	3–5 days			
Prasugrel	P2Y12 irreversible inhibitor	7–10 days	7 days			

LT- Liver transplantation; PCC: prothrombin complex concentrates; FFP- fresh frozen plasma; CrCl: creatinine clearance; aPCC: activated prothrombin complex concentrate; DDVAP: desmopressin.

or thrombocytopenia with platelet transfusions prior to LT is not recommended. POC care of testing like ROTEM and TEG should be used to detect and guide intraoperative management of coagulopathy.

Recommendations

26. *For patients receiving anticoagulants, we recommend that anticoagulant drugs should be stopped before LT and bridging therapy with LMWH should be initiated. We recommend against the routine use of blood products for the reversal of anticoagulation except in an emergency setting (strong, level C)*
27. *We recommend that a short course of DAPT for 30 days is sufficient duration in patients with newer-generation DES listed for LT following which aspirin monotherapy should be continued. A multidisciplinary decision involving cardiology is necessary for optimizing DAPT therapy to balance the risk of surgical bleeding with stent thrombosis. (strong, level B). Routine correction of thrombocytopenia/platelet dysfunction with platelet transfusion* prior to LT is not recommended *(strong, level C).*

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