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Evaluation of recipients with significant comorbidity – Patients with cardiovascular disease

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Summary

Liver transplant(ation) (LT) is the most effective treatment for patients with decompensated liver disease. The increasing prevalence of obesity and type 2 diabetes and the growing number of patients with non-alcoholic fatty liver disease being evaluated for LT, have resulted in a greater proportion of LT candidates presenting with a higher risk of cardiovascular disease. As cardiovascular disease is a major cause of morbidity and mortality after LT, a thorough cardiovascular evaluation pre-LT is crucial. In this review, we discuss the latest evidence on the cardiovascular evaluation of LT candidates and we focus on the most prevalent conditions, namely ischaemic heart disease, atrial fibrillation and other arrhythmias, valvular heart disease, and cardiomyopathies. LT candidates undergo an electrocardiogram, a resting transthoracic echocardiography and an assessment of their cardiopulmonary functional ability as part of their standardised pre-LT work-up. Further diagnostic work-up is undertaken based on the results of the baseline evaluation and may include a coronary computed tomography angiography in patients with cardiovascular risk factors. The evaluation of potential LT candidates for cardiovascular disease requires a multidisciplinary approach, with input from anaesthetists, cardiologists, hepatologists and transplant surgeons.

Introduction

The increasing rates of obesity and the growing prevalence of non-alcoholic fatty liver disease (NAFLD) as an indication for liver transplant(ation) (LT) has led to a greater proportion of LT candidates presenting with a higher risk of, or with established, cardiovascular disease. Cardiovascular complications are the leading cause of non-graft-related mortality in the early period after LT.[1] Cardiovascular morbidity and mortality is even more prevalent more than a year after transplantation, even in patients with no identified pre-existing risk factors.[2] Hence, a thorough pre-transplant cardiovascular evaluation of potential recipients is warranted. In this review, we focus on the cardiovascular assessment of LT candidates, particularly functional assessment and the evaluation and management of the most common cardiovascular comorbidities, namely coronary artery disease, atrial fibrillation and arrhythmias, valvular disease, and cardiomyopathies. The evaluation and management of portopulmonary hypertension and hepatopulmonary syndrome are beyond the remit of this review.

Cardiovascular risk assessment of the LT candidate

LT candidates undergo an electrocardiogram (ECG) and resting transthoracic echocardiography as part of their standardised pre-LT work-up. Clinical history can identify cardiovascular risk factors, such as obesity, type 2 diabetes, hypertension, hyperlipidaemia, past history of smoking or familial history of early cardiovascular disease. Although patients with non-alcoholic steatohepatitis (NASH)-related cirrhosis are considered at high risk of developing cardiovascular events both before and after LT, there is insufficient evidence to recommend a specific risk algorithm.[3] Further diagnostic work-up is undertaken based on the results of the baseline evaluation described above. In Fig. 1, we present an indicative algorithm for cardiovascular assessment of the LT candidate.

Assessment of cardiopulmonary reserve and functional ability

Notably, baseline assessment does not provide complete information on the ability of individuals to use oxygen in stress-induced conditions such as surgery or infections. For this purpose, dynamic tests of the so-called *cardiopulmonary reserve*, which can be defined as aerobic exercise capacity, that integrate the responses of different systems (such as the cardiovascular, pulmonary, neurological and skeletal muscle) are required (Fig. 2).

It is useful to remember that in the resting state, Fick's equation describes the different components of oxygen uptake (VO_2):[4] VO_2: $VO_2 = (SV * HR) * (CaO_2 - CvO_2)$

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Key points

- LT candidates undergo electrocardiogram, a resting transthoracic echocardiography and an assessment of their cardiopulmonary functional ability as part of their standardized pre-LT work up.
- Further diagnostic work-up is undertaken based on the results of the baseline evaluation and may include a coronary computed tomography angiography in patients with cardiovascular risk factors.
- The evaluation and decision-making regarding transplant eligibility of patients at higher cardiovascular risk is not standardized and varies depending on local resources and expertise.
- EF<40 %, severe valvular disease not amenable to repair prior to LT, severe pulmonary hypertension, significant coronary artery disease and symptomatic ventricular arrhythmias that cannot be controlled are all contraindications to LT.
- The evaluation of potential LT candidates for cardiovascular disease requires a multidisciplinary approach, with input from anaesthetists, cardiologists, hepatologists and transplant surgeons.

where SV is the stroke volume, HR is the heart rate, CaO_2 is the arterial oxygen content, and CvO_2 is the mixed venous oxygen content. Hence, VO_2 is the product of cardiac output times the arterial minus mixed venous oxygen content.

Metabolic equivalents (METs) express the resting oxygen uptake in a sitting position normalised to body weight and expressed in ml per minute. One MET equals 3.5 ml/kg/min.[4]

At maximal exercise, the Fick's equation reflects the maximal capacity of the individual to take in, transport and use oxygen and defines the functional aerobic capacity of the individual: $VO_2max = (SVmax * HRmax) * (CaO_2max - CvO_2max)$.

Functional cardiopulmonary reserve is impaired in patients with decompensated chronic liver disease;[5] in a systematic review evaluating patients listed for LT, the mean peak VO_2 across studies was 17.4 ml/kg/min,[6] which is below the threshold of 18 ml/kg/min required for normal independent living. This could result from several factors related to the decompensated stage of cirrhosis that affect different systems and organs[7];[8]: i) circulatory system (hyperdynamic circulation due to portal hypertension, cirrhotic cardiomyopathy [CCM]); ii) respiratory system (hydrothorax, hepatopulmonary syndrome, portopulmonary

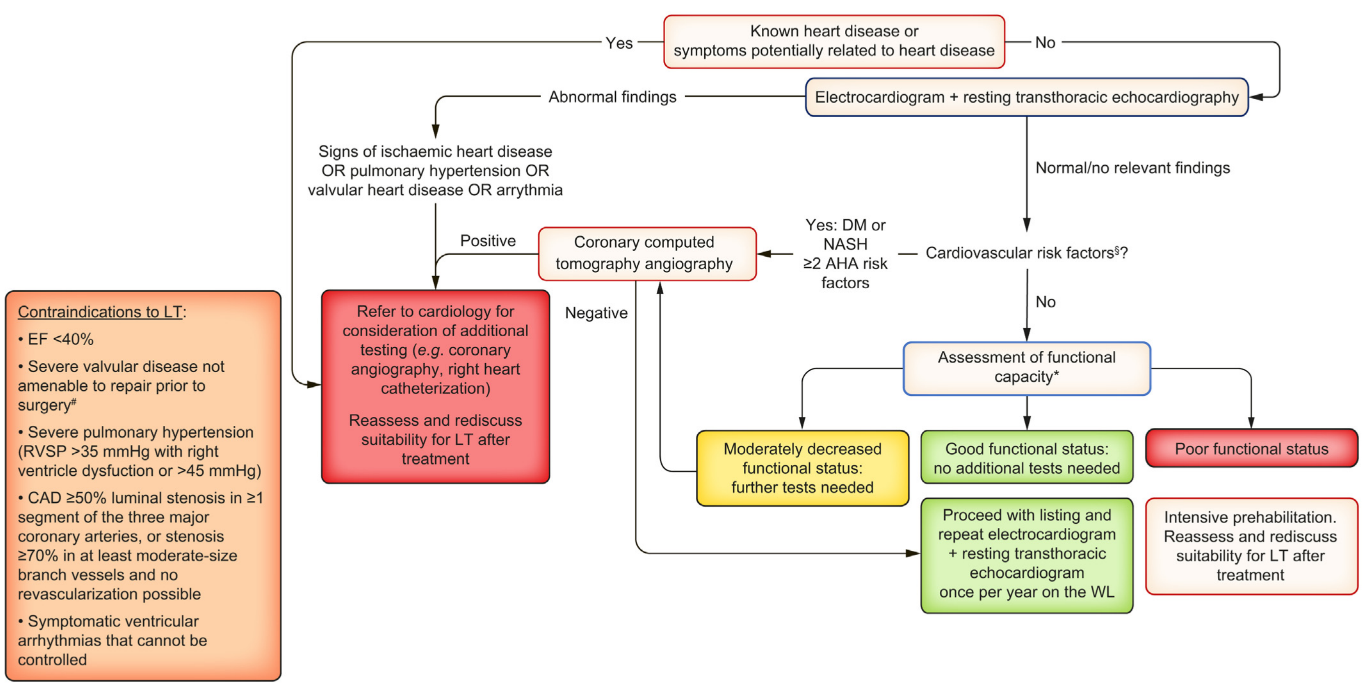

Fig. 1. Indicative algorithm for cardiovascular work-up in patients listed for liver transplantation. #If severe aortic stenosis, consider transcatheter aortic valve replacement. §AHA risk factors: Age (>50 years); family history of heart disease; dyslipidemia, history of hypertension, chronic kidney disease, left ventricular hypertrophy, family history of premature CHD, active or past tobacco use, or prior coronary artery calcification score >0. *If CPET is available, the following threshold values can be used: Peak VO_2 >26 ml/kg/min (men) or >21 ml/kg/min (women): Good functional status Peak VO_2 21–26 ml/kg/min (men) or 17.5–21 ml/kg/min (women): Moderately decreased functional status (moderate risk) Peak VO_2 <21 ml/kg/min (men) or <17.5 ml/kg/min (women): Poor functional status If 6MWT is chosen, the following threshold values can be used[13]: 6MWD >450 m: Good functional status 250-450 m: Moderately decreased functional status <250 m: Poor functional status CAD, coronary artery disease; DM, diabetes mellitus; EF, ejection fraction; NASH, non-alcoholic steatohepatitis; RVSP, right ventricular systolic pressure; 6MWT, 6-minute walk test.

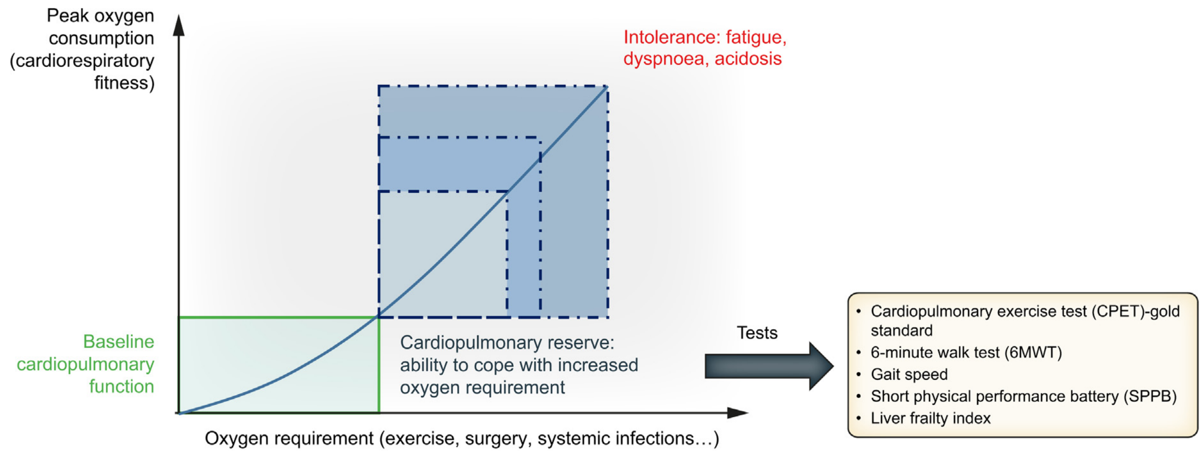

Fig. 2. The concept of cardiopulmonary reserve. This refers to the ability to increase peak oxygen consumption (y axis) with increasing oxygen requirements (x axis). There are several tests to assess cardiopulmonary reserve in a liver transplant candidate, such as the cardiopulmonary exercise test, the 6-minute walk test, gait speed, short physical performance battery and the liver frailty index.

hypertension); iii) skeletal muscle system (malnutrition, sarcopenia, obesity and sedentary behaviour).

In addition to the above, patients with underlying cardiovascular disease might show further decreased cardiopulmonary reserve due to features specific to their underlying disease process. Whenever cardiopulmonary reserve is impaired, mitochondrial capacity to use oxygen is reduced at a tissue level (skeletal muscle; cardiac muscle), and tissues are unable to adapt to pathophysiological stresses.

Not surprisingly, several studies have demonstrated that decreased cardiopulmonary reserve (also referred to as "deconditioning") is associated with mortality both on the LT waiting list and after LT, independently of liver function[9];[6].

Objective tools to study the cardiopulmonary reserve include cardiopulmonary exercise testing (CPET – the reference standard) and indirect tests, which have the advantage of being inexpensive and simpler to apply. In general, all the described tests are highly reproducible and have been extensively validated in the setting of chronic extrahepatic diseases and in the geriatric population.

Liver frailty index, a simple test aiming at quantifying physiological reserve, will be discussed in another review from this special issue.

Reference standard: cardiopulmonary exercise testing

CPET is performed in an exercise/physical medicine setting, and requires dedicated resources and expertise.[4] The testee exercises on a treadmill or stationary bicycle, and during cardiac, blood pressure, pulse oximetry and expired gas analysis monitoring, the workload is increased until exhaustion.[6] The data output include the ventilatory anaerobic threshold and peak exercise oxygen uptake (VO_2), as well as minute ventilation/carbon dioxide production gradient and slope (the latter seems to be superior in characterising muscle deconditioning in the general population). In patients awaiting LT, the anaerobic threshold on CPET predicts pre- and post-transplant survival; however, the thresholds vary significanly among publications.[6];[10] Data on the ability of CPET to predict intra- or post-operative cardiovascular events is not available in the current literature.

The advantage of CPET is that it provides granular data on cardiopulmonary reserve. Disadvantages include the complex infrastructure required (which may not be widely available), cost, and the practicality of patients with severe decompensated liver disease performing the test. Thus, although CPET is incredibly important in facilitating our understanding of cardiopulmonary reserve in patients awaiting LT, it has not been widely adopted as a screening tool to assess cardiovascular risk across transplant centres.

6-Minute walk test

As its name suggests, the 6-minute walk test (6MWT) measures the distance walked on a flat surface for 6 min. It is designed to measure functional exercise capacity in the cardiology and thoracic medicine setting,[11] and has been validated as a predictor of mortality in patients with cirrhosis awaiting LT.[12] A recent study in 694 patients awaiting LT showed that for every 100-metre increase in 6MWT, there was a significant decrease in mortality (hazard ratio 0.48).[13] A cut-off threshold of 250 m is associated with increased waitlist mortality.[12]

Although the data derived is not as detailed as the CPET, advantages of the 6MWT are the ease, wide availblility and relatively low cost of the test. Disadvantages include the inability to accommodate physically impaired individuals and the challenges of testing severely ill indivduals.

In conclusion, there is clear evidence that patients with poorer cardiopulmonary reserve have worse waitlist outcomes, and tests aimed at quantifying cardiopulmonary reserve are an important part of risk stratification of candidates for LT. Interventions aimed at improving cardiopulmonary reserve are needed. Published studies investigating "pre-habilitation" (including 2-50 patients, largely with well-compensated cirrhosis), utilise exercise-based interventions (mostly supervised and hospital-based) to improve debility and to some extent cardiopulmonary reserve.[14] The combination of aerobic and resistance exercises at moderate-high intensity appears most effective in improving physical debility.[14] In another small study, a 12-week home-based physical activity programme combined with essential amino acid supplementation (12 g/day) improved aerobic fitness in patients with cirrhosis and poor cardiopulmonary reserve.[15]

Experience of CPET in this context is severely limited owing to limited access to the test. Thus, other functional tests should be utilised to determine who may benefit from intervention. These tests should not necessarily preclude patients as transplant candidates but serve as tools to inform risk-based discussions and to plan interventions.

Evaluation of LT candidates for coronary heart disease

The prevalence of coronary heart disease (CHD) in patients with end-stage liver disease (ESLD) is higher than in the general population.[16–19] This increased risk may be partly explained by systemic inflammation that contributes to thrombo-inflammation.[20] LT candidates with CHD are at high risk of intra-operative, perioperative and long-term complications, including death.[21,22] The term CHD refers to both macrovascular and microvascular diseases of the myocardium, although the primary focus of most practice guidance recommendations on CHD in LT candidates is on epicardial coronary artery obstruction. Herein, CHD is defined as a history of myocardial infarction, revascularisation (coronary artery bypass grafting or percutaneous coronary intervention) or known ≥50% stenosis in a major epicardial coronary artery. CHD screening refers to testing modalities (*e.g.*, non-invasive stress tests) used to detect the presence of previously unknown but clinically significant CHD.

The optimal approach to CHD evaluation and management in LT candidates has been debated for decades, with multiple guidelines and consensus statements published (Table 1).[23–30] There remains controversy related to *who* to screen, *how* to screen, and *why* to screen and treat chronic CHD in LT candidates. A major goal of CHD risk stratification is to identify patients who may be at risk of perioperative death, to improve assessment of the intermediate risks and benefits of LT, and to guide better medical or interventional management for long-term risk mitigation. There are two epidemiologic trends in LT that influence current recommendations for CHD screening: changing LT demographics leading to an increasing prevalence of CHD risk factors (*e.g.*, older age, higher prevalence of NASH),[31] and improved medical management of CHD leading to declining rates of CHD-related morbidity with a concurrent rise in rates of non-coronary cardiac events after LT.[32,33] Results of CHD screening in LT candidates should inform considerations regarding the benefit of LT, perceived risk of perioperative complications and projected long-term outcomes.[34]

Table 2 outlines the test characteristics of different screening approaches for prediction of significant CHD and

Table 1. Published recommendations or suggestions for coronary heart disease screening in asymptomatic liver transplant candidates, 2011–2022.

Guideline or statement	Society	Recommendations: Initial evaluation	Recommendations: Surveillance after listing
Raval *et al.* State-of-the-Art 2011[23]	American College of Cardiology (ACC)	• Perform ICA in candidates with CAD, DM, or ≥2 risk factors • Risk factors: age (male >45 years; female >55 years), hypercholesterolemia, hypertension, smoking, family history of early CAD • CCTA may be an acceptable alternative in select patients	Not discussed
Lentine *et al.* Scientific Statement 2012[24]	American Heart Association/American College of Cardiology Foundation (AHA/ACCF)	• Consider non-invasive stress testing in candidates without active cardiac conditions based on presence of ≥3 risk factors regardless of functional status (Class IIb | Level of Evidence C) • Risk factors: DM, CAD, >1 year on dialysis, left ventricular hypertrophy, age >60 years, smoking, hypertension, dyslipidemia	Not discussed
Martin *et al.* Clinical Practice Guidelines 2014[25]	American Association for the Study of Liver Diseases (AASLD)	• Assess cardiac risk factors and perform stress echocardiography in all candidates (Strength of Recommendation 1 | Quality of Evidence B) • Perform invasive coronary angiography as clinically indicated (Strength of Recommendation 1 | Quality of Evidence B) • Consider cardiac revascularisation in LT candidates with significant coronary artery stenosis (>70% stenosis) prior to transplant (Strength of Recommendation 2 | Quality of Evidence C)	Not discussed
Kristensen SD *et al.* Guidelines on non-cardiac surgery 2014[126]	European Society of Cardiology (ESC) and European Society of Anaesthesiology (ESA)	• Clinical risk indices are recommended to be used for perioperative risk stratification (Class I | Level B) • Assessment of cardiac troponins in high-risk patients, both before and 48-72 h after major surgery, may be considered (Class IIb| Level B) • NT-proBNP and BNP measurements may be considered for obtaining independent prognostic information for perioperative and late cardiac events in high-risk patients (Class IIb | Level B) • Pre-operative ECG is recommended for patients who have risk factors(s) [+] and are scheduled for intermediate- or high-risk surgery (Class I | Level C) • Rest echocardiography may be considered in patients undergoing high-risk surgery (Class IIb | Level C) • Imaging stress testing is recommended before high-risk surgery in patients with more than two clinical risk factors[+]and poor functional capacity (<4 METS) (Class I| Level C) • Imaging stress testing may be considered before high- or intermediate-risk surgery in patients with one or two clinical risk factors[+] and poor functional capacity (<4 METS) (Class IIb | Level C) • Indications for pre-operative coronary angiography and revascularisation are similar to those for the non-surgical setting (Class I | Level C)	Not discussed

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Table 1. (*continued*)

Guideline or statement	Society	Recommendations: Initial evaluation	Recommendations: Surveillance after listing
EASL Clinical Practice Guidelines 2015[27]	European Association for the Study of the Liver (EASL)	• Perform electrocardiogram and transthoracic echocardiography in all candidates to rule out underlying heart disease (Grade II-3) • Perform cardiopulmonary exercise testing in patients with multiple risk factors or age>50 years to uncover asymptomatic IHD. If the target heart rate is not achieved during a standard exercise test, a pharmacological stress test is the test of choice (Grade II-3)	Not discussed
VanWagner *et al.* Consensus Recommendations 2018[28]	American Society for Transplantation (AST)	• Consider invasive or non-invasive angiography if known CAD, abnormal non-invasive test, or a high pretest probability of CAD (*e.g.*, DM or ≥2 traditional risk factors) (2C) • Risk factors: age (male >45 years; female >55 years), hypercholesterolemia, hypertension, tobacco use, family history of early CAD • The decision to pursue stress testing should be based on individualised evaluation of the candidate's pretest probability for having CAD (1C)	Not discussed

Cheng *et al.* Scientific Statement 2022[30]	American Heart Association (AHA)	• All LT candidates without known CHD should have a cardiac physical exam, ECG, and a resting TTE, with further testing guided by risk stratification
		  o In LT candidates who are at high risk for significant CHD (diabetes or NASH or ≥2 other CHD risk factors*), anatomic coronary imaging is recommended.
		  o In LT candidates who are low risk for significant CHD (age<40 years, able to achieve ≥4 METs, no NASH or diabetes, no CHD risk factors*), no further cardiac stress testing may be needed if initial ECG and resting TTE are normal.
		  o In LT candidates who are intermediate risk, stress imaging alone can be considered.
		• ICA should be the last procedure performed in the evaluation prior to listing for LT after a patient has already been deemed an acceptable transplant candidate. Multidisciplinary discussions are necessary prior to performing therapeutic ICA in LT candidates to ensure there is agreement as to the management plan if disease is detected.
		  o In LT candidates with kidney dysfunction, ICA or CCTA may be safely performed. Consultation with nephrology and steps to minimise contrast-induced acute kidney injury should be employed.
		  o In LT candidates, ICA may be performed despite coagulopathy. Routine transfusion of blood products to a target or platelet count is not recommended. Multidisciplinary discussion with hematology when appropriate, is warranted to guide peri-procedural transfusions.
			Reassessment after listing should include at least annual risk assessment** for underlying CHD, along with ECG and resting TTE at a minimum. Perioperative and post-operative management of high-risk cardiac risk LT recipients should include a Cardiologist, with additional subspecialist involvement as needed.

AASLD, American Association for the Study of Liver Diseases; ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; AHA, American Heart Association; AST, American Society for Transplantation; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; DM, diabetes mellitus; EASL, European Association for the Study of the Liver; ECG, electrocardiogram; ICA, invasive coronary angiography; IHD, ischaemic heart disease; LT, liver transplant(ation); METs, metabolic equivalent tests; TTE, transthoracic echocardiogram.

*CHD risk factors include any of the following: hyperlipidaemia/dyslipidaemia, hypertension/history of hypertension, chronic kidney disease, left ventricular hypertrophy, family history of premature CHD, active or past tobacco use, coronary artery calcification score >0.

**Risk assessment includes repeat consideration of dynamic changes in CHD risk factors or recalculation of risk scores. The level of repeat anatomic or stress imaging should be considered on a case-by-case basis.

***Not specific to LT candidates.

+Clinical risk factors according to the revised cardiac risk index: IHD (angina pectoris and/or previous myocardial infarction), heart failure, stroke or transient ischaemic attack, renal dysfunction (serum creatinine >170 umol/L or 2 mg/dl or a creatinine clearance <60 ml/min/1.73 m2) or diabetes mellitus requiring insulin therapy.

CHD events. Traditional CHD risk factors (male sex, hypertension, hyperlipidaemia, smoking, age >60 years, left ventricular hypertrophy, prior cardiovascular disease or diabetes mellitus) are the strongest predictors of moderate coronary artery stenosis (≥50% stenosis) in LT candidates; LT candidates with three or more traditional CHD risk factors are most likely to have obstructive CHD (sensitivity and specificity 75% and 77%, respectively)[17,35,36] and cardiac events after LT.[37] Two or more CHD risk factors exhibited a sensitivity of 75% for the prediction of obstructive CHD, but a specificity of only 60%, and may not reliably predict post-LT cardiovascular events[36] .[30] NASH, the second leading and fastest growing indication for LT in the US and Europe,[38,39] is an independent risk factor for both obstructive CHD and adverse cardiac outcomes after LT; when added to traditional CHD risk factors, a NASH diagnosis improves specificity for obstructive CHD and prediction of post-LT events.[30,32,40] Various biomarkers (*e.g.*, troponin-I,[41] high-sensitivity c-reactive protein[42]) may also predict CHD risk in LT candidates, although their ability to reclassify risk beyond established CHD risk factors has not been confirmed.[37] Coronary artery calcium score (CACS) has a strong negative predictive value (NPV: 95-100%) for significant CHD, and could thus be incorporated into algorithms to risk stratify LT candidates.[43–46] In one study, a threshold CACS of 251 maximised the sensitivity and specificity for detection of obstructive CHD, while a CACS >400 predicted both the need for revascularisation and early complications after LT.[44,45] The 'CAD in LT' (CAD-LT) score (available at www.cad-lt.com) predicts significant (*e.g.*, obstructive) CHD (internal cross-validation c-statistic, 0.76), and may obviate the need for

Table 2. Test characteristics for prediction of significant CHD or post-operative CHD or CV events in LT candidates.

Test strategy	Threshold/abnormality	Predictive ability for significant CHD	Predictive ability for post-operative CHD or CVEs
Resting ECG	Positive CAD ECG = Q wave, ST segment depression, and/or pathologic T wave		Standardised incidence ratio: 5.01 (95% CI 3.91–6.34)[127] aHR 2.91, 95% CI 1.43-5.92[128]
Functional testing			
Dobutamine stress perfusion	Abnormal if delay in resting replenishment of myocardial contrast following high mechanical index impulse of >4 s under resting conditions or >2 s at peak stress	Unknown	aHR 7.5, 95% CI 1.9–30.7[129]
DSE	Positive DSE: new or worsening wall motion abnormalities	Pooled sensitivity 25% (95% CI 9–51) Pooled specificity 68% (95% CI 44–84) Diagnostic OR 0.79 (95% CI 0.12–3.84)	No association
SPECT	Positive MPI: variable per study as some considered only reversible perfusion defects positive, with fixed defects or normal perfusion being considered negative, others listed having one or more area of ischaemia	Pooled sensitivity 62% (95% CI 37–83) Pooled specificity 60% (95% CI 39–79) Diagnostic OR 2.5 (95% CI 1.7–5.64)[49,130] AUC: 0.649	No association (random-effects RR: 2.64, 95% CI 0.67, 10.4, I^2 = 34.9% (moderate heterogeneity))
Stress CMR	Positive stress CMR: Perfusion deficit on CMR using regadenoson/adenosine (patients with eGFR >30 ml/min/m^2; 86%) or dobutamine (patients with eGFR ≤30 ml/min/m^2; 9%)	Sensitivity: 50% Specificity: 98% Accuracy: 98%[60]	No association
CPET	No consistent CPET parameters/cut-off values provided[6] Baseline VO_{2peak} was reported in five studies (weighted mean 17.4 +/- 1.9 ml/kg/min) Baseline AT reported in four studies (weighted mean 11.6 +/- 0.7 ml/kg/min)	Not evaluated for obstructive CAD	Not evaluated for CVEs Sensitivity and Specificity of VO_{2peak} cut-offs for prediction of post-transplant mortality: 1) VO_{2peak} ≤17.6 ml/kg/min: Sensitivity 67%, Specificity 77%[131] 2) VO_{2peak} < 14 ml/kg/min: Sensitivity 86%, Specificity 45%[132] 3) VO_{2peak} < 60% predicted: Sensitivity 86%, Specificity 64%[10]
Angiography			
Coronary Computed tomography angiography (CCTA)	Obstructive CAD: coronary plaque ≥1 mm and a ≥50% reduction in luminal stenosis in ≥1 segment of the three major coronary arteries	Unknown	NPV of 95% [0.82-0.99] for CVEs NPV 100% [0.85-1.00] for coronary events[64] Post-op MI specifically Sensitivity 20.0% Specificity 91.2% PPV 6.2% NPV 97.5% Accuracy 89.1% aOR: 2.37; 95% CI 1.18–4.45; p = 0.010)[71]
Invasive coronary angiography (ICA)	≥50% stenosis in LAD or RCA, or stenosis ≥70% in at least moderate-size branch vessels requiring intervention with PCI with or without balloon angioplasty	Gold standard	Normal ICA, HR: 1.35, 95% CI 0.79–2.33; p = *0.298*; Non-obstructive CAD, HR: 1.53, 95% CI 0.84–2.77; p = 0.161; Significant CAD, HR: 1.96, 95% CI 0.93–4.15; p = 0.080[133] Meta-analysis: random-effects RR: 2.14, 95% CI 0.78–5.83, I^2 = 0%[130]
Biomarkers			
Any arterial calcification	Presence of arterial calcification on low dose CT in any location (aortic, coronary artery, or peripheral artery)	Any arterial calcification (OR 6.30, 95% CI 0.77–52.06, p = 0.09)	No difference in intraoperative CVEs (4.7% *vs.* 2.9%, p = 0.55) Significant difference in cumulative post-LT admission CVEs (22.3% *vs.* 9.7%, p = 0.007)

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Table 2. (*continued*)

Test strategy	Threshold/abnormality	Predictive ability for significant CHD	Predictive ability for post-operative CHD or CVEs
CACS	CAC >100	Sensitivity: 100% Specificity: 28%[45]	No association
	CAC >400	Sensitivity: 100%	CVE OR, 4.62; 95% CI 1.14–18.72, p = 0.032[44]
		Specificity: 44%	CAC >400 *vs.* CAC=0 for post-op MI (IPTW-aOR 2.6, 95% CI 1.51–4.58; p = 0.001)[71]
Troponin-I	TnI >0.07 ng/ml	Unknown	HR 2.00, 95% CI 1.13–3.56, p = 0.023[134]
hsCRP	hsCRP >3.0 mg/dl	Unknown	HR 1.03, 95% CI 1.00–1.05, p = 0.047[42]
Scoring systems			
Traditional CHD risk factors	≥2	75% sensitivity 60% specificity	Not associated
	≥3	75% sensitivity 77% specificity	HR, 2.39; 95% CI 0.99–5.77, p = 0.044
		OR 1.72, 95% CI 1.12–2.65 per risk factor	AUC: 0.76
CAD-LT score[47]	Age Gender DM HTN Tobacco pack years Family history of CAD Personal history of CAD	AUC: 0.76 (95% CI 0.72–0.80) Sensitivity: 21%, Specificity: 96%	Unknown
CAR-OLT score[135]	Age Sex White/black *vs.* other race Not working for income Lower education Pulmonary hypertension No HCC HTN Diabetes HF Respiratory failure on ventilator	Unknown	AUC: 0.78
MELD+Revised Cardiac Risk Index[136]	High-risk surgery History of ischaemic heart disease HF Cerebrovascular disease, DM requiring insulin Creatinine >2	Unknown	AUC: 0.80 (95% CI 0.726–0.874)
Framingham risk score	Sex Age (30-74 years) BMI Systolic blood pressure DM Anti-HTN treatment Smoking status	Unknown	HR, 1.06; 95% CI 1.02–1.09; p <0.003[137] AUC: 0.71[138]
SCORE[138]	Gender Age (40-65 years) Total cholesterol SBP Smoking status	Unknown	AUC: 0.80
PROCAM[138]	Gender Age (35-65 males; 45-65 females) LDL HDL Triglycerides SBP Smoking status DM Family history of CAD	Unknown	AUC: 0.78

aHR, adjusted hazard ratio; CACS, coronary artery calcification score; CAD, coronary artery disease; CHD, coronary heart disease; CMR, cardiovascular magnetic resonance imaging; CPET, cardiopulmonary exercise testing; CV, cardiovascular; CVE, cardiovascular event; DM, diabetes mellitus; DSE, dobutamine stress echo; ECG, electrocardiogram; HDL, high-density lipoprotein; hsCRP, high-sensitivity c-reactive protein; LDL, low-density lipoprotein; LT, liver transplant(ation); MELD, model for end-stage liver disease; OR, odds ratio; PCI, percutaneous coronary intervention; RR, relative risk;SBP, systolic blood pressure; SPECT, single photon emission computerized tomography.

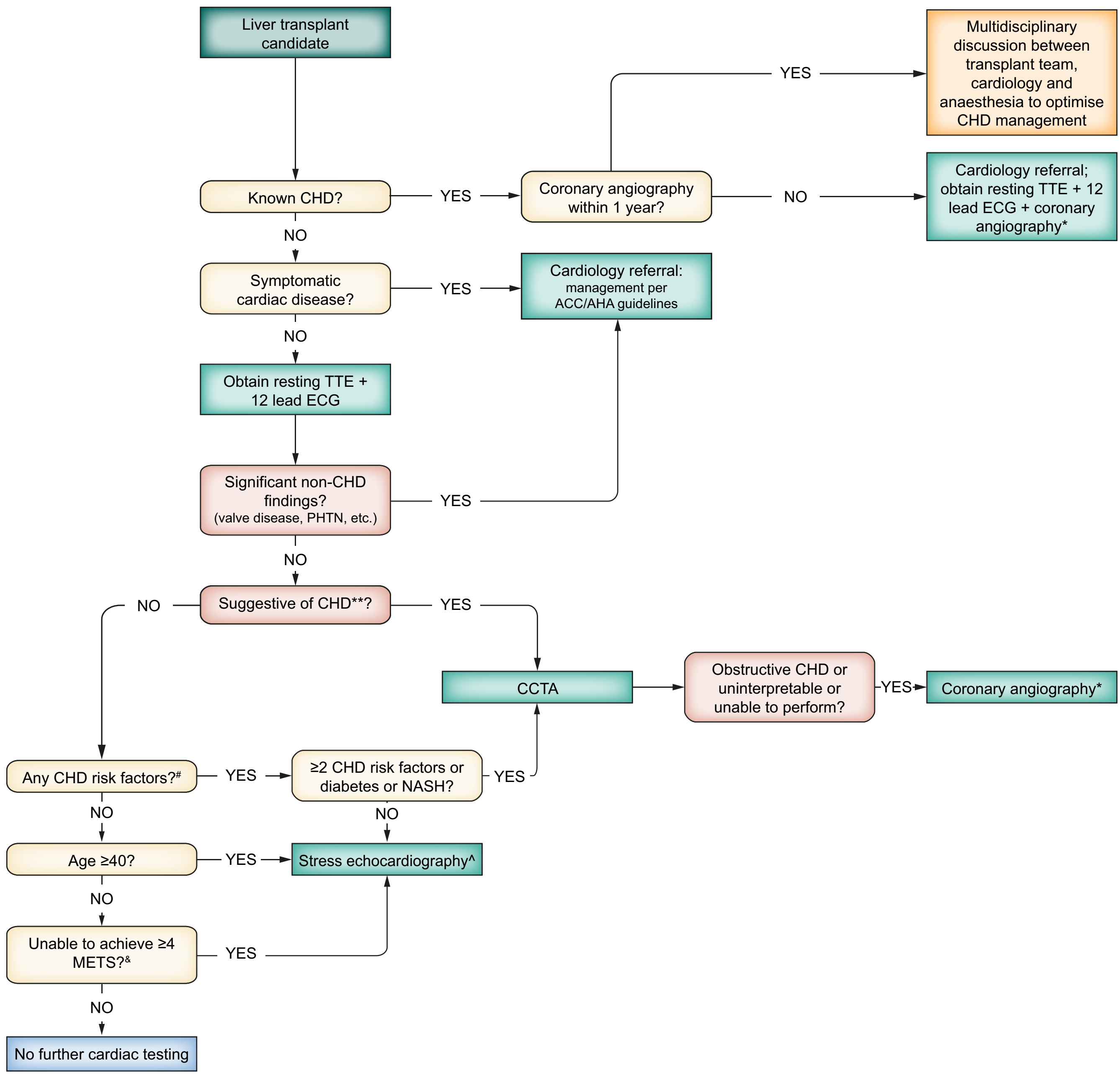

Fig. 3. Proposed approach for CHD screening in asymptomatic LT candidates. Known CHD is defined as a history of MI, revascularisation (CABG or PCI), or known >50% stenosis in a major epicardial coronary artery. Symptomatic cardiac disease is defined as angina, angina-equivalent, or any possible symptoms referrable to known CHF, arrhythmias, or valvular disease. *Choice of modality based on patient characteristics and centre experience. **Suggestive of CHD: silent MI on ECG or TTE with new or unexpected regional left ventricular wall motion abnormality or new or unexpected left ventricular systolic dysfunction (LVEF <50% or absolute global longitudinal strain <18%). #CHD risk factors: dyslipidemia, HTN history, chronic kidney disease, left ventricular hypertrophy, family history of premature CHD, active or past tobacco use, coronary artery calcification score >0. &≥4 METs: Patient can climb ≥1 flight of stairs without stopping or walk up hill for ≥1-2 blocks or scrub floors or move furniture or golf, dance, run or play tennis. ^SE: exercise SE preferred; dobutamine SE if patient cannot exercise; consider cardiac PET as an alternative if available. In patients whose critical illness precludes SE, consider CCTA or coronary angiography (choice of modality depending on patient and centre factors). ACC/AHA, American College of Cardiology/American Heart Association; CCTA, coronary computed tomography angiography; CHD, coronary heart disease; CHF, congestive heart failure; ECG, electrocardiogram; LT, liver transplant; LVEF, left ventricular ejection fraction; MET, metabolic equivalent; MI, myocardial infarction; NASH, non-alcoholic steatohepatitis; PET, positron emissions tomography; (P)HTN, (portal) hypertension; RV, right ventricle; RVSP, right ventricular systolic pressure; SE, stress echocardiography; TTE, transthoracic echocardiogram.

invasive coronary angiography (ICA) without increasing the risk of CHD events.[47]

A risk-based approach should be considered to guide further testing for CHD in asymptomatic LT candidates (Fig. 3). Evidence supports angiography (non-invasive or invasive) over universal stress imaging in intermediate- or high-risk LT candidates.[28,31] Low-risk patients may not require additional testing.[48]

Both pharmacologic and exercise stress testing have low sensitivity (13-37%) and suboptimal NPVs (75-80%) for detection of significant CHD[49] and prediction of post-operative CHD events in LT candidates.[50] This is due to blunted chronotropy (which makes it difficult to reach the target heart rate) and reduced cardiorespiratory fitness in ESLD.[50–57] Resting vasodilation in ESLD also limits the predictive accuracy of myocardial perfusion scintigraphy.[58] Cardiac magnetic resonance stress imaging has an excellent NPV of 98% in LT candidates, but its use is limited by its high cost, requirement for significant centre expertise, and overall low sensitivity (50%) for CHD.[59,60] In the general population, cardiac positron emission tomography (PET) with calculation of myocardial flow reserve detects coronary ischaemia with high accuracy.[61] PET perfusion imaging is highly attractive in LT candidates given its renal safety profile and the fact that it is not affected by chronic vasodilation, though data evaluating its use is limited.[62]

Non-invasive angiography with coronary computed tomography angiography (CCTA) should be considered as the initial testing strategy in LT candidates who are at high risk for significant coronary artery disease (CAD).[30,31,49,63,64] CCTA is contraindicated (or impractical) in patients with a severe or anaphylactic allergy to contrast media, atrial fibrillation, or intolerance to beta blockers. While both CCTA and ICA are associated with nephrotoxicity, the risk of nephrotoxicity may be lower with CCTA.[65,66] Coronary angiography may be performed in LT candidates with kidney dysfunction in consultation with a nephrologist.[26,28] When an ICA strategy is chosen, it may be performed despite coagulopathy in patients with ESLD.[67,68] However, periprocedural risks exist, so ICA should be reserved as the last test performed in an otherwise appropriate candidate for LT listing.[69] Notably, anatomic evaluations may miss functional microvascular disease that can contribute to type 2 myocardial infarction after LT.[70,71] However, universal functional testing is not supported by data incorporating cost-effectiveness and utility measures.[57] Therefore, stress testing alone should be reserved in intermediate risk patients (Fig. 2).

Under current US allocation policies based on acuity circles, some patients (*e.g.*, those with model for end-stage liver disease [MELD] exceptions) may wait for over a year for LT.[72] CHD risk will not be static over that time and thus risk assessment should be considered at least yearly. The intensity of repeat testing will depend on both patient and programmatic factors, but should include assessment of change in prevalence or severity of CHD risk factors and risk factor control, at the minimum. This recommendation is in line with US practice patterns, where 85% of transplant centres repeat risk assessment with an ECG and resting echocardiography at least yearly.[31]

Patients with high MELD who present simultaneously for LT evaluation and the operation can be in varying levels of decompensation, with fluctuating levels of stress-induced cardiac ischaemia and other cardiac abnormalities.[73] Studies do not distinguish between outpatient and inpatient evaluations for CHD. Therefore, the timing, selection, and interpretation of testing must take the severity of the patient's illness and the stage of cirrhosis at the time of evaluation into consideration.

Data to support or refute routine revascularisation prior to LT are limited. If CHD is identified, management decisions (*e.g.* regarding medical and percutaneous interventions, or surgical revascularisation) must be made in conjuction with cardiologists and specialists in thoracic surgery, in the context of a high-risk patient population being considered for a lifesaving and resource-intensive LT procedure.[30] In LT candidates, significant CHD (≥50% luminal stenosis in ≥1 segment of the three major coronary arteries, or stenosis ≥70% in at least moderate-size branch vessels) without revascularisation options should be considered a contraindication to LT.[30,74,75] Table 3 summarises management considerations for identified CHD in LT candidates based on currently published practice guidance. Importantly, this discussion regarding the evaluation of CHD risk is not relevant to patients with *symptomatic* CHD, in whom immediate evidence-based interventions for acute coronary syndrome should be considered.

Cardiac arrhythmias

Cardiac arrythmias are common among LT candidates and recipients, and have been associated with major adverse cardiovascular events (MACEs), including stroke and decreased post-LT survival.[32,76–84] While both atrial and ventricular arrythmias occur, atrial fibrillation (AF) remains the most common arrythmia in this setting, and is the entity for which the most data is available in the LT population.

Atrial fibrillation

In data from systematic reviews and meta-analyses, the prevalence of pre-existing AF prior to LT (∼3-6%), as well as post-operative AF (up to 10%), appears to be higher than rates in the general population (which are reported to be 1-2% below age 65 and 9% over 65).[77,84,85] AF is likely the most common MACE to occur in the early post-operative period, accounting for 43% of MACEs in the first 90 days post-LT in an analysis of UNOS (United Network for Organ Sharing) data.[32] As LT candidates get older and develop more significant cardiac comorbidities, AF is likely to be even more common.

Risk factors for pre-existing AF in LT candidates include elevated BMI, hypertension, diabetes mellitus, CHD, and prior cerebrovascular accidents.[77] It has also been hypothesised that AF may be a manifestation of underlying CCM, which is an increasingly recognised factor in LT patient outcomes. It is also notable that both isolated intraoperative[81] or new/persistent post-LT AF[82,86] appear to be associated with important clinical events, including MACEs, post-LT kidney dysfunction, length of hospital stay and survival. Reported risk factors for post-LT AF include age, BMI, MELD score at LT, diabetes mellitus, pre-LT AF, CHD, and perioperative factors including the use vasopressors prior to LT and pulmonary artery diastolic pressure at the end of the LT surgery.[76,79,80,82,85,87] Risk indices for post-operative AF have been developed, including in a large single-centre experience, wherein patients with the high-risk index had a more than 60% chance of developing post-LT AF.[82] This type of risk stratification could be used to drive monitoring or perhaps preventative therapies.

In terms of screening, identification of patients with AF in the pre-LT period and/or with CCM is essential. While all patients undergo an ECG in the LT evaluation process, this may not be sensitive in the setting of paroxysmal AF and has not been extensively studied in the context of LT risk stratification. Given the high index of suspicion that is required, confirmatory ECGs should be performed if tachycardia is noted in follow-up visits or if tachycardia or an irregular rhythm is noted on physical examination. In addition, ambulatory monitoring is at times needed to diagnose arrhythmias, in consultation with a cardiologist, for patients with symptoms that warrant this evaluation.[85] Similarly, patients at high risk, including those with transient AF during the

Table 3. Considerations for management of asymptomatic identified CHD in LT candidates.

Strategy	Clinical considerations
Goal-directed medical management	*Statins* - In LT candidates, statin therapy should be based on risk and not lipid levels, especially since lipid profiles do not accurately capture CHD risk in patients with ESLD.[139] - In advanced liver disease, including compensated cirrhosis, statins appear safe and beneficial although the risk of muscle-related side effects is higher and may be additive to risk conferred by other factors. - In LT candidates with Child-Pugh class A or B cirrhosis and clinical CHD, evidence favours statin use for secondary prevention with close monitoring of liver chemistries and markers of rhabdomyolysis.[140] - In patients with acute or acute-on-chronic liver failure, or in those with decompensated Child-Pugh class C cirrhosis, statins should not be used for secondary prevention of asymptomatic CHD due to the higher risk of toxicity.[140] *Anti-platelet agents* - There are no data to support an absolute platelet threshold for safety of aspirin use in LT. Thus, risk of bleeding and benefit of aspirin for secondary prevention of CHD events should be considered on a case-by-case basis. - To reduce risk of bleeding in LT candidates with an indication for DAPT, use of a proton pump inhibitor to prevent development of upper gastrointestinal bleeding and minimisation of duration of DAPT are recommended.[30] *Beta blockers* - Beta blockers may be beneficial in selected LT candidates, with consideration for carvedilol in patients with CHD and compensated cirrhosis.[140] - Peritransplant, patients on chronic beta-blocker therapy should be continued on beta blockers, in line with guidance in the general population.[141] - No data exist to support the initiation of beta-blocker therapy for primary prevention of perioperative cardiovascular events in LT candidates. *RAAS blockers* - The safety of RAAS blockade is limited in LT candidates due to the physiology of ESLD and should be avoided in patients with decompensated cirrhosis or around the time of LT.
Revascularisation	There are no prospective randomised trials of CHD revascularisation in LT candidates; however, the presence of angiographically significant stenoses increases the risk of cardiac events and death after LT.[37] Revascularisation of asymptomatic significant CHD should be performed only if the patient has been deemed to be a suitable LT candidate because routine treatment is associated with significant risk without clear benefit.[30] Percutaneous coronary intervention can be safely performed in LT candidates.[133] According to recent consensus guidance, in LT candidates with significant CHD requiring revascularisation, newer-generation drug-eluting stents with a minimum of 3 months of DAPT should be used if possible. In LT candidates who cannot wait to complete guideline-recommended duration of DAPT, options include consideration of drug-eluting stents with a very short duration of DAPT (1 month), bare metal stent if available for use, or combined LT-CABG. LT candidates with significant CHD without revascularisation options should be considered to have prohibitively high risk for LT.[30]

CHD, coronary heart disease; DAPT, dual anti-platelet therapy; ESLD, end-stage liver disease; LT, liver transplantation; RAAS, renin angiotensin aldosterone system.

LT surgery or hospitalization, require ongoing monitoring and the consideration for addition of rate control agents to prevent hemodynamically significant episodes.

The management of AF in LT recipients warrants further investigation. No large-scale clinical trials of prevention or management in the setting of transplant have occurred. Thus, recommendations are extrapolated from the non-transplant setting.[88,89] The mainstays of current AF treatment recommendations include rate (and/or rhythm) control as well as antithrombotic therapies. In terms of rate control, consensus and guideline recommendations focus on the use of beta blockers or calcium channel blockers, depending on ejection fraction and the clinical scenario,[88,89] both of which are frequently deployed in the setting of post-LT AF. Use of these agents is an important consideration in the perioperative period, particularly among patients with pre-LT AF who may be on these agents chronically. Pre-emptively choosing beta blockers for the management of hypertension in patients at higher risk of AF may be beneficial. Anti-arrhythmics such as amiodarone may be required for patients intolerant or resistant to rate control, though prolonged use of amiodarone is often avoided pre- and post-transplant due to the potential for hepatotoxicity.[83,86] Occasionally, more intensive therapies are required when the limits of medical management are reached, including direct-current cardioversion or catheter ablation, especially among perioperative patients who do not tolerate beta blockade due to hypotension. However, there are no data in the LT population or in the immediate post-operative period to direct the utilisation of these approaches.

Finally, the use of antithrombotic therapy is an important consideration in the treatment of AF that must be based on an individualised assessment of the risk of stroke and bleeding. The risk of thromboembolic stroke in patients with post-LT AF may be up to 8-fold higher than in those without AF, and traditional risk stratification approaches including CHA_2DS_2VASc may help to guide the use of anticoagulation in this setting.[78,90] The HAS-BLED score may be used for bleeding risk assessment,[91] especially as liver function is considered in this model, though surgeons should be consulted regarding the initiation of anticoagulation and surgical bleeding risk in the immediate post-operative period. The availability of direct oral anticoagulants (DOACs) has been a major advance in the antithrombotic approach in AF, as these agents have been shown to have superior efficacy and safety compared to warfarin, and overall fewer drug-drug interactions, in the non-transplant setting. However, DOAC pharmacokinetics are influenced by liver function, and patients with advanced liver disease were excluded from the pivotal trials.[92] While the European Medicines Agency and the US Food and Drug Administration have not restricted the use of DOACs in patients with Child-Pugh class A cirrhosis, for Child-Pugh B cirrhosis, rivaroxaban and edoxaban are contraindicated, while dabigatran and apixaban may be used with caution. In Child-Pugh class C cirrhosis, DOACs are associated with a high risk of spontaneous bleeding events and are contraindicated.[87,93] Thus, caution should be exercised if DOACs are needed in patients with advanced liver disease pre-LT, and in the dynamic perioperative period.

While AF is relatively common among transplant candidates and recipients, it rarely precludes LT if multidisciplinary care can provide sufficient rate control and no additional cardiac comborbidities such as heart failure or significant valvular dysfunction exist.

Ventricular arrythmias and sudden cardiac death

Ventricular arrythmias are less well studied in the context of advanced liver disease and LT. Symptomatic premature ventricular contractions in a patient with a structurally normal heart may be treated with beta blockade,[94] though CCM should be considered in this setting. Otherwise, patients with symptomatic ventricular arrhythmias that cannot be controlled are not generally considered candidates for isolated LT, thus data on risk stratification and management are not available.

There is a growing body of literature regarding post-LT sudden cardiac death. The rates of cardiac arrest/ventricular arrythmias among LT recipients may be 4-folder greater than in other non-cardiac surgeries.[1,95,96] While the reasons for this are uncertain, an increase in the QT interval (a known risk factor for ventricular arrhythmias) has been associated with CCM. A recent model has been developed to predict cardiac arrest following LT, the cardiac arrest risk index.[97] This point-based index includes QTc, MELD score, age and sex, with a score ≥3 representing those at high risk of these events. This risk stratification may allow for more vigilance in this population, including peri-LT surveillance, minimisation of medications that prolong QT interval, and the potential use of beta blockers for those at the highest risk.

Valvular heart disease

The routine use of echocardiography for LT assessment can lead to the diagnosis of asymptomatic valvular heart disease. NAFLD in particular is associated with 33% higher odds for the development of aortic valve sclerosis,[98] whereas the presence of NAFLD is an independent predictor of calcifications in the aortic and mitral valves in patients with type 2 diabetes.[99] The presence of severe valvular heart disease is a contraindication to LT. Surgical valve repair pre-LT is extremely high risk, with 30-day mortality of over 30% in patients with Child-Pugh B and C cirrhosis.[100] In a cohort study of 57 patients undergoing open heart surgery, an MELD score of 13.5 could predict post-operative in-hospital mortality with an area under the curve of 0.85.[101] Herein, we will focus particular attention on aortic stenosis. The presence of severe mitral or tricuspid regurgitation is often associated with pulmonary hypertension and is thus beyond the scope of this review.

The emergence of the transcatheter approach to aortic valve repair provides a potential bridge to LT in candidates with severe aortic stenosis. Studies in non-cirrhotic patients at low surgical risk suggest that transcatheter aortic valve repair (TAVR) is equivalent[102] or even better[103] than surgical repair. In the setting of cirrhosis, data is limited. In a series of 105 patients with cirrhosis undergoing aortic valve replacement, surgical replacement and TAVR were associated with acceptable and comparable short-term outcomes.[104] Among patients with a MELD ≥12, survival after valve replacement was not superior to medical management alone.[104] Similarly, in a cohort of 85 patients with cirrhosis of variable severity, intraoperative mortality after TAVR or surgical repair was 18.8%, though TAVR was associated with favourable long-term survival compared to surgical repair.[105] The above suggests that in patients with Child-Pugh B and C cirrhosis, aortic valve replacement should be considered only if LT is a realistic option. Ten cases of TAVR to restore LT candidacy in patients with critical aortic stenosis and decompensated liver disease were recently reviewed; all but one patient were successfully transplanted.[106] Such cases require a multidisciplinary approach with input from cardiologists, interventional radiologists and cardiac surgeons.

Heart failure and cardiomyopathies

Overt heart failure is uncommon in patients undergoing evaluation for LT, as those with poor heart function are unlikely to be referred unless it is for combined heart-liver transplantation. However, subclinical cardiac dysfunction is prevalent and frequently asymptomatic due to inactivity and poor exercise tolerance attributed to ESLD. Specifically, CCM is noted in 20-47% of patients listed for LT depending on the underlying disease and comorbidity (NASH 47%, ALD 33%, other aetiologies 20%).[107] The physiologic milieu is well described in recent reviews and is beyond the scope of this discussion.[108,109] CCM generally denotes asymptomatic (subclinical) cardiac dysfunction (both systolic and diastolic dysfunction with insufficient response to stress) directly linked to cirrhosis and portal hypertension.[110] CCM criteria (Box 1) have been revised with the advent of improved diastolic dysfunction metrics and should be specifically sought in all potential transplant recipients.[108] Subclinical cardiac dysfunction impacts post-LT outcomes, with pre-LT diastolic dysfunction predictive of post-LT cardiovascular disease[107] and post-LT heart failure associated with decreased survival.[111] The *'reversibility'* of CCM after LT has been brought into question and cannot be assumed, as the physiologic changes associated with CCM can lead to myocardial fibrosis which may be irreversible.[107,112] The hyperdynamic state of portal hypertension and cardiac function may take up to 6-12 months to

Box 1. Cirrhotic cardiomyopathy diagnostic criteria (2020)[108]

Systolic component:

- Reduced LVEF (<50%), or
- Decline in GLS (absolute value <18)

Diastolic component:

Three of the following:

- Early diastolic transmitral flow to early diastolic mitral annular tissue velocity (E/e') ≥15
- Left atrial volume index >34 ml/m^2
- Septal e' <7 cm/second
- Tricuspid regurgitation maximum velocity >2.8 m/second in the absence of pulmonary hypertension

When diastolic dysfunction is diagnosed: severity can be determined by E/A ratio (0.8-2 = grade II and >2 = grade III).

Patients with only two out of the four criteria need further echocardiographic evaluation to define diastolic dysfunction and its grade.

recover.[113] Careful cardiac follow-up after LT is therefore highly recommended, with annual echocardiography until normalisation of systolic and diastolic function.[114]

Pre-LT cardiac function assessment is largely performed by transthoracic echocardiography (TTE) but because of the decrease in systemic vascular resistance (afterload) associated with ESLD, left ventricular ejection fraction (EF) is frequently inflated and may not identify the true cardiac dysfunction that can manifest once a normal afterload is restored. EFs are commonly expressed as a volumetric EF (three dimensional) or linear EF (one dimension), with the former being the more accurate measure (that may differ from the latter). Thus, EF is not the only metric of focus on the TTE and assessment for diastolic dysfunction, myocardial strain and possibly left atrial dysfunction is of particular importance.[107,115] According to American and European cardiology guidelines, an EF of >50% is considered preserved and an EF of <50% is considered reduced (>60% is considered hyperdynamic). Data in LT recipients has suggested an EF of <60% to be associated with an increased risk of post-LT MACE[41] and worse post-transplant survival,[116] likely reflecting hyperdynamic measures of true cardiac dysfunction. Thus, one could argue that post-transplant echocardiographic follow-up be considered in individuals with a pre-LT EF of <60% to optimise post-transplant cardiac function. Guidance documents suggest that an EF of <40% is an absolute contraindication to LT; EFs between 41-49% are a relative contraindication and warrant routine follow-up TTE every 6 months in LT candidates.[28,108] An EF of <50% that does not increase with stress may also identify a subset of high-risk patients within this category and could be considered a contraindication to LT.

Cirrhosis is not the only factor associated with cardiac dysfunction. Obesity, diabetes, hyperlipidemia and hypertension are highly prevalent in western countries (and particularly highly prevalent in patients with NASH seeking transplant), while coronary artery disease (a well-established risk in such patients) can lead to ischaemic cardiomyopathy. Severe alcohol-related cardiomyopathy is uncommon in individuals with advanced alcohol-related liver disease, but those with liver disease are more likely to have a less severe asymptomatic myocardial dysfunction. This can manifest with myocardial fibrosis-associated impaired systolic function and left ventricle dilation.[117] Patients with alcohol-related cirrhosis and heavy alcohol use are also at increased risk for CAD[118](possibly exacerbated by hypertension and cigarette smoke exposure in some studies), heart failure, cerebrovascular and peripheral-vascular disease.[119] Haemochromatosis is an uncommon cause of advanced liver disease nowadays but does confer an associated risk of co-existing cardiac disease due to iron deposition in the myocardium and conduction system. This cardiac involvement is associated with a significant increase in mortality after LT.[120] Most commonly, patients with cirrhosis will have rhythm disturbances (tachyarrhythmias, premature ventricular beats, nodal block) and less commonly overt heart failure or pulmonary hypertension. TTE may show increased atrial and ventricular mass, and diastolic dysfunction with or without left ventricular dysfunction. The cardiomyopathy can be of a restrictive or dilated pattern.[121]

Unrelated to specific liver disease aetiologies is hypertrophic cardiomyopathy, an autosomal dominant disorder of myocardial hypertrophy that can be associated with left ventricle outflow tract obstruction in 0.2% of the general population and 0.5% of patients evaluated for LT.[122] This entity can be further impacted by superimposed CCM (diastolic and systolic dysfunction) and the low systemic vascular resistance and hyperdynamic state characteristic of ESLD.[123,124] Perioperative and in-hospital post-transplant cardiac complications and mortality are significantly increased with hypertrophic cardiomyopathy, with data suggesting that it increases the in-hospital mortality associated with non-cardiac surgery by as much as 61%.[124] Not surprisingly, early post-operative mortality is significantly increased in LT surgery, with 1-year and 5-year mortality rates of 33% and 39%, respectively, largely predicted by the left ventricular outflow obstruction gradient.[123,125] Notably, an inducible left ventricle outflow obstruction on stress, present in up to 40% of individuals on the LT waiting list, may not portend as poor a prognosis, with only transient intraoperative hypotension but no significant impact on post-operative outcomes.[122]

Diagnosis and management of cardiac dysfunction in transplant candidates

Diagnosis of cardiomyopathy revolves around the TTE and the stress response to exercise as discussed. The hyperdynamic state of the patient with end-stage cirrhosis, unfortunately, results in an under-recognition of cardiac dysfunction and intra-operative and post-operative risk. While on the waiting list, physical exercise and consideration of more aggressive cardiopulmonary rehabilitation are warranted, given data in the cardiac literature.

Unmet needs in cardiovascular assessment

Many gaps in the LT literature are due to the low number of affected patients, relative to cohorts in the cardiac literature, which makes large randomised-controlled studies unfeasible in this setting. Data often revolves around retrospective studies (both small single-centre and larger database studies) or small prospective single-centre studies. The challenges of cardiovascular evaluation in the hyperdynamic state of patients with cirrhosis cannot be translated from the existing cardiac literature. The data in the transplant literature is heavily biased, as it reflects only patients getting listed and receiving a LT in a risk averse environment (due to organ stewardship and punative oversight metrics). There is severely limited data on patients referred for evaluation that do not make the waitlist. Hence, this literature can only guide us in identifying individuals thought to be well enough to survive transplantation who may have had a suboptimal outcome. Optimising access to LT for patients with underlying cardiac disease/dysfunction will require better non-invasive testing, specific to this population, that is easily accessible and can identify patients with high perioperative risk. Beyond perioperative survival, these pre-transplant cardiac functional assessments should help us to identify individuals at high risk of post-operative outcomes and better manage these patients to prevent these outcomes.

Conclusions

The evaluation of potential LT candidates for cardiovascular disease requires a multidisciplinary approach, with input from anaesthetists, cardiologists, hepatologists and transplant surgeons. The evaluation and decision-making regarding transplant eligibility of patients at higher cardiovascular risk is not standardised and varies depending on local resources and expertise. It is unclear what combination of risk factors should trigger further investigations, as shown for instance in Table 2 for the screening of CHD. Despite the high prevalence of asymptomatic cardiac disease in LT candidates, the potential harm and costs of universal screening may outweigh the potential benefits. However, given limited availability of deceased donor organs for transplant, screening may identify patients deemed to be at excessive risk of cardiac-related adverse outcomes (regardless of intervention) for whom transplantation may not yield sufficient benefit to justify use of a scarce organ. The growing prevalence of obesity, type 2 diabetes and NAFLD will result in even higher risk candidates in the future and will necessitate robust protocols for assessment and testing. It will also require more pro-active strategies to reduce cardiovascular morbidity and mortality after LT.

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Abbreviations

AF, atrial fibrillation; CACS, coronary artery calcium score; CAD, coronary artery disease; CCM, cirrhotic cardiomyopathy; CCTA, coronary computed tomography angiography; CHD, coronary heart disease; CPET, cardiopulmonary exercise testing; EF, ejection fraction; ECG, electrocardiogram; ESLD, end-stage liver disease; ICA, invasive coronary angiography; LT, liver transplant(ation); MACEs, major adverse cardiovascular events; MELD, model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NPV, negative predictive value; PET, positron emission tomography; TAVR, transcatheter aortic valve repair; TTE, transthoracic echocardiography.

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