Cardiac Evaluation Guidelines for NZLTU

Discussion Document

Cardiovascular disease is a leading cause of morbidity and mortality following liver transplantation. The rate of early (30-day and <6-month) major adverse cardiac events (MACE) after liver transplantation (LT) is estimated at 10-20%, with wide variation in reported incidence depending on the definitions used. If a cardiac event occurs post-transplantation, 1-year and longer-term patient and graft survival is likely to be worse [1-6]. While coronary artery disease (CAD) is a key focus in our pre-operative evaluation, the importance of assessing for cirrhotic cardiomyopathy, heart failure, atrial fibrillation, valvular pathology, portopulmonary hypertension and hepatopulmonary syndrome is well recognised.

The AASLD 2013 guideline stipulates "the purpose of cardiac evaluation prior to liver transplantation is to assess [and optimise] perioperative risk, and exclude concomitant cardiopulmonary disorders that would preclude a good long-term outcome" [7].

Coronary Artery Disease

The evidence for investigation and treatment of stable CAD in the community and prior to non-cardiac surgery has prompted a shift away from intervention, with a focus on medical optimisation. This is largely based on the CARP[π] and ISCHAEMIA[Ω] trials indicating a lack of benefit in reducing early (30-day) cardiac events, with potential risk of harm from surgical delay and unnecessary intervention [8, 9]. However, this evidence does not inform which strategy is optimal in the longer 2-5 year term, or how applicable it is to extrapolate to specific very high risk surgical groups [10, 11]. Additionally, while non-invasive stress testing was inadequate in these studies, the FAME trials[Σ] support using FFR to better assess functionally significant disease, with FFR (≤0.80) guided PCI in addition to best available medical therapy reducing the need for urgent revascularisation at 1 and 5 years [12, 13].

Evidence informing best treatment of chronic coronary syndrome in liver transplant patients is even more limited. There are few small observational studies, that are increasingly not generalisable to current advancements in PCI and new generation DES, nor candidate populations who are increasingly older, with a greater prevalence of metabolic syndrome and NASH as the primary cause of cirrhosis. However, in the absence of specific evidence, extrapolation from the general population to liver transplant candidates is cautioned on the basis that:

[π] CARP showed that revascularisation did not improve survival in patients with stable 1- or 2-vessel CAD.

[Ω] The ISCHEMIA trial suggests that in patients with stable CAD and moderate-severe ischemia on non-invasive testing (excluding left main stem disease), early revascularisation with a PCI did not result in a significant difference in major cardiac events, compared to optimal medical therapy. Those who received PCI had relatively more frequent peri-procedural myocardial infarctions/events, balanced by relatively fewer long-term (median 3.2 year) events.

[Σ] The FAME and FAME-II trials suggest selective FFR guided PCI for coronary lesions is associated with fewer major cardiac events compared to optimal medical therapy alone. In the 5-year follow-up the difference in major cardiac events was largely driven by a difference in urgent PCI, rather than a difference in cardiac mortality or MI.

1. *The prevalence of cardiac disease and complications is greater*

   Patients with cirrhosis have a higher risk of significant cardiac disease than the general population, with moderate-severe CAD reported in as many as 1 in 4 liver transplant candidates [14-16], with variations noted between patient groups and transplant programmes [17-20]. Observational studies indicate the presence of CAD increases the risk of early (30-day and 1-year) post-LT mortality, but it is inconsistently associated with the severity or extent of CAD, with variable utilisation of revascularisation and medical optimisation [21, 22]. The significance was first recognised by Plotkin in the 1990s, liver transplant recipients with CAD having a 50% 3-year mortality and 80% morbidity in survivors [23]. Awareness has led to improvements in the practice of selecting and optimising liver transplant candidates [24], but significant uncertainty remains in how to diagnose the burden of CAD in asymptomatic patients without complication, and then whether the associated risk of diagnosed disease is either modifiable or prohibitive to proceeding with LT.

2. *There are unique physiological changes related to ESLD*

   Physiological sequalae from ESLD is well described, with high cardiac output, low systemic vascular resistance, and enhanced sympathetic nervous activation. This can have broad ranging implications, including:

   - The reduced cardiac reserve of ESLD patients means a cardiac event is more likely to be associated with a poor prognosis [6].
   - Interpretation of a 'normal' EF on resting echocardiogram may not be applicable. A single large retrospective study of over 2799 liver transplant (mostly living donor) patients in South Korea with a MELD ≥ 20 and EF ≤ 60% had significantly higher 90-day and median 5.4-year all-cause mortality [3].
   - Limitations in the reliability of stress testing interpretation are well described, with a high degree of baseline vasodilatation and impaired chronotropy.
   - Non-specific symptoms such as dyspnoea, and impaired exercise capacity due to general deconditioning, severely limit the ability to diagnose significant cardiac disease. Consequently the absence of cardiac symptoms has less predictive value in transplant candidates than in the general population [18].

3. *Liver transplant surgery is physiologically stressful*

   Liver transplant surgery can be a massive physiological insult, in excess of regular moderate exertion or the majority of other non-cardiac surgery. There is a potential for major intravascular shifts, transient severe anaemia, arrhythmias, vasoplegia, severe instability at the time of reperfusion, prolonged surgical times (>6hrs), delayed graft function, and post-operative hypercoagulability. The high prevalence of metabolic syndrome and renal dysfunction post-transplantation also means this cardiac risk is ongoing long after transplantation.

4. *Organs are a scare resource*

   Unique to a liver transplantation programme, in addition to our duty of care to only offer liver transplant to candidates who are predicted to experience an improved 5-year survival, there is a requirement to ensure organs are allocated to those candidates with a realistic chance of good survival. The cost of a bad outcome post-transplantation not only affects the primary patient being treated, but a secondary patient who could have benefited from receiving the graft as well.

The flow diagram outlining the proposed NZLTU cardiac evaluation of CAD prior to liver transplantation is provided in Appendix 1. The following outlines the rationale behind this in more detail:

Risk Factor assessment: functional status predicts outcome, but not the presence of CAD in ESLD patients.

Functional capacity

The approach to cardiac evaluation of patients having non-LT surgery emphasises assessment of functional status and the presence of cardio-respiratory symptoms, and is shifting away from a reliance on non-invasive stress testing in favour of biomarkers to risk-stratify patients and determine the level of post-operative surveillance required [25]. This approach is supported by the METS study[ª], but this study was noted to include a relatively low risk population [26]. Therefore, the ability and appropriateness of extrapolating this approach to liver transplant candidates is unknown.

Impaired aerobic capacity is relatively common in liver transplant candidates, and multiple single-centred trials have shown that it has predictive value for the post-transplantation course when measured with CPET (evidence summarised in Appendix 2) or the 6-minute walk test. Carey et al. identified a 6-minute walk distance <250m was associated with a high risk of death post-LT, each 100m increase in distance increasing survival by an adjusted 42% [27]. In a systematic review of CPET by Ney et al. post-transplant mortality was predicted by the anaerobic threshold (AT), with an AT difference of 2.0 between survivors and non-survivors, but due to heterogeneity across studies optimal thresholds could not be determined [28]. Prentis et al. reported a ROC-derived AT of <9mls/kg/min was predictive of 1-year mortality post-LT, but this is one of the smaller studies available, and further research is required to validate that threshold [29].

Risk indices

A recent systematic review of 29 studies attempted to identify risk factors in the LT population consistently associated with cardiovascular events post-LT [4]. Older age and prior history of cardiovascular disease were the most consistent predictors of cardiovascular events. However, notable variability between the studies limits the ability to draw substantive conclusions[Δ]. Alexander et al. help to validate the AHA/ACCF 2012 recommendation of requiring ≥3 risk factors to predict severe CAD, although this was a small single centre of only 220 transplants, with only a modest discrimination, with an AUROC of 0.77 (75% sensitivity, 77% specificity)[30].

Risk prediction models for various early (30-day to 12-months) adverse cardiac events following LT have been attempted, all with insufficient accuracy (summarised in Appendix 2).

Biomarkers

Biomarkers may have a role in predicting cardiovascular events and mortality following LT. A recent study showed elevated pre-LT high sensitivity cardiac troponin I)was associated with significantly higher all-cause

[ª] The METS study was a multicentre prospective cohort study of over 1400 patients, evaluating the ability of clinician-assessed functional capacity, Duke Activity Status Index (DASI) questionnaire, NT pro-BNP, and CPET to predict perioperative cardiovascular events within 30-days of major elective non-cardiac surgery. The DASI questionnaire was the only assessment shown to improve prediction of 30-day death or myocardial infarction, and myocardial injury. NT pro-BNP predicted 30-day death or myocardial injury and 1-year mortality.

[Δ] Age was the most consistently identified risk factor, in multivariate analysis in 8 of the 22 studies, but was still not significant in the majority (14 of the 22 studies).

30-day and 1-year mortality [31]. However, limitations[y] with the study are noted, with a currently conflicting body of evidence [32, 33].

BNP levels may correlate with the severity of cirrhosis, or the presence of cirrhotic cardiomyopathy, rather than simply with ischemic heart disease [34]. High quality prospective analysis of the prognostic utility of BNP in LT is currently lacking, but a prospective observational trial of 207 LT patients showed a pre-LT BNP >155 pg/mL was associated with a 27% early mortality rate [35].

Non-invasive cardiac testing: DSE or CTCA is used to screen patients with risk factors for CAD.

The 2013 AASLD guidelines recommend stress echocardiogram for all liver transplant candidates, using exercise if functional status allows, suggesting pharmacological (dobutamine) stress if required [7]. The AHA/ACCF 2012 Expert Consensus Document only recommend screening with non-invasive stress tests when there are ≥3 of the following risk factors: diabetes mellitus, prior cardiovascular disease, left ventricular hypertrophy, age >60yrs, smoking, hypertension, and dyslipidaemia [15]. Since these guidelines were published, the use of CTCA and biomarker screening has been established in the general surgical population. While there is significant variation between centres internationally, most centres use non-invasive investigations to screen for the likelihood of CAD, to minimise the number of patients exposed to the risks of invasive coronary angiography.

Historically, the two most common non-invasive tests used to screen for CAD in LT candidates without active cardiac conditions are nuclear myocardial perfusion imaging (MPI) and dobutamine stress echocardiography (DSE). The current literature base (summarised in Appendix 2) is inconsistent, being limited to mostly small single-centre observational studies, with heterogeneity between studies in terms of the indications for non-invasive testing and definitions for 'significant' CAD or 'major cardiac events'. However, the general indication is that these tests have limited diagnostic value for severe CAD in ESLD, DSE being less sensitive but more specific than MPI with dobutamine, it being variably reported as to which has a better negative predictive value [36, 37]. Interestingly with graded exercise stress, echocardiogram and perfusion imaging have similar sensitivity and specificity for significant CAD. The major limitation of DSE is the high rate of equivocal tests (failure to reach >80% of maximum predicted heart rate, or <18,000 rate-pressure product [38, 39]) due to chronotropic incompetence, however some studies have shown that in advanced liver failure this in of itself is predictive of a serious cardiovascular event [40-42].

CTCA provides a radiological estimate of the location and severity of CAD, with a reported negative predictive value of 83-99% for excluding significant CAD [43]. A recent metanalysis in the general population also confirmed the high negative predictive value of CTCA in predicting MACE, and that it is at least as comparable to other stress testing modalities[Σ] [44]. The evidence is still limited in liver transplant patients, with no reports comparing the diagnostic accuracy (for CAD) of CTCA compared with invasive coronary angiography. A small study reported a high degree of sensitivity and negative predictive value (95%) for major cardiac events post-LT [45]. Considering the factors that interfere with the diagnostic quality of CTCA images (i.e. a

[y] This was a single centre South Korean study of 487 patients with a large proportion of live donors. Patients with known coronary artery disease were excluded, and troponin levels were usually measured the day prior to surgery, limiting generalisability to use at the time of listing in our local programme.

[Σ] The presence of any CAD on CTCA predicted perioperative MACE with a sensitivity of 89% and specificity of 35%; or obstructive CAD predicted perioperative MACE with a sensitivity 70% and specificity 60%.

tachycardiac or irregular cardiac rhythm, the inability to lie still and breath hold, obesity), the feasibility of testing in ESLD could be a concern, but early studies have not indicated this is the case.

CT coronary calcium score (CCS) is a noncontrast study that provides a global estimate of coronary calcification and atherosclerotic burden, rather than indicating specific anatomical lesions [43]. A cumulative CCS score is provided in Agatston units, a score ≥400 units indicating severe disease warranting diagnostic evaluation, 100-399 indicating moderate (clinically significant) disease warranting aggressive risk factor management, and 0 indicating a very low probably of coronary disease in an asymptomatic patient [46]. Again, there is little evidence in the liver transplant population, but CCS may have some utility in predicting cardiac events following LT, a CCS >400 was significantly associated with major cardiac complications 30-days post-LT in a retrospective review of 443 LT patients [47].

It must be noted that negative non-invasive testing (or invasive angiogram excluding severe obstructive disease) does not rule out clinically relevant CAD. Underlying mild-moderate obstructive CAD is still at risk of plaque rupture or vasospasm, with diffuse mild disease having implications for long-term survival and therefore suitability for transplantation.

Revascularisation: conflicting evidence, but pre-transplant PCI may be appropriate for severe CAD.

The AASLD 2013 guidelines recommend "revascularisation of significant coronary artery stenosis (>70% stenosis) may be attempted prior to LT, although rigorous proof of benefit in asymptomatic recipients is lacking"[7].

Maddur et al. justified their increasingly invasive institutional practice with less reliance on stress testing, in a retrospective review of over 1200 transplants between 2000-2010 in a single US centre [48]. Over 400 patients had an angiogram and 57 required PCI (35 with a negative stress test) prior to transplantation. The 10-year study period was split into 3 subperiods defined by changes in practice, an increase in the rate of catherization and PCI in each period being significantly associated with a reduction in 1-year all-cause mortality and post-operative MIs. While PCI and medical optimisation was standardised, the study design did not account for other changes in clinical practice that could explain the outcome improvement, and while the patients appeared to be older and more comorbid in the later cohorts, surgical and immunosuppression advances likely contribute to at least some of the observed improvement[∞].

In contrast, a retrospective review by Snipelisky et al. cautioned that intervention does not modify all-cause or cardiac-cause mortality rates in candidates with moderate-severe coronary artery disease [49]. While it included over 2000 transplants between 2000-2010 in a single US centre, who all had a DSE prior to transplant, only 51 had an angiogram within 6 months of transplantation. Of the 23 patients with moderate-severe disease, 7 had bypass surgery and 3 had percutaneous intervention (stent type not specified), with no defined protocol to inform invasive treatment or medical optimisation. Those with severe CAD had higher rates of cardiac death (but not all-cause death); and 50% of those with coronary intervention died of cardiac related causes, with no cardiac deaths in the non-intervention group.

[∞] In those with a positive stress echocardiogram or symptoms, stenosis >50% was treated. In those with negative stress tests and no clinical symptoms, stenosis >50% in the LAD or RCA or >70% stenosis in at least a moderate size branch vessel was treated. 4 patients had disease not amenable to PCI and were referred for bypass grafting. Mostly BMS, but 50% of cases in the middle phase were 1st generation DES. 40 single vessel, 14 2-vessel stenosis, 3 with 3-vessel stenosis.

In another retrospective review Wray et al. proposed that coronary artery disease did not affect 1-year and 3-year all-cause mortality due to successful revascularisation prior to LT. Across seven US institutions between 1998-2010, it included 630 patients who had an angiogram prior to OLT, 151 of whom had obstructive CAD (>50% stenosis), 96 with severe (>70%) and 77 with multivessel disease [50]. 74% of those with severe disease had interventions, over half of all interventions being with PCI, mostly using BMS, and 40% with bypass surgery, including five cases of cardiac surgery at the time of transplantation. Screening criteria for angiogram, medical optimisation and treatment of CAD was not standardised across institutions, with no reporting of cardiac morbidity or cardiac death in this group of angiogramed patients, nor the whole transplant population in this time period. Satapathy et al. similarly concluded that patients with revascularized CAD have a comparable post-transplant survival to patients without known obstructive CAD on the basis of stress testing [2]. However this single US centre retrospective study had an even smaller sample of patients, with 87 of a total 1500+ liver transplants having a pre-operative angiogram, and only 29 of these having obstructive CAD (>50% stenosis), 22 of whom were revascularised at various time points prior to transplantation, including 10 who had bypass surgery 2-32yrs prior. While a standard cardiac assessment pathway was described, deviations due to clinical judgement were noted, with no mention of medical optimisation. The small sample size and significant limitations of a retrospective study design, severely limits our ability to make any definite conclusions about the adequacy of these group's cardiac evaluation and management of liver transplant patients.

Case series with no more than 30 patients report successful outcomes following simultaneous cardiosurgical procedures and LT in Child Pugh A patients, with medium- and long-term survival outcomes variably comparable to those having transplantation alone [51-54]. We have the capability for this at Auckland, but local experience is limited, and suitability would be holistically considered in a multidisciplinary forum.

Most liver transplant programmes worldwide have tended towards relatively aggressive revascularisation strategies, enabling an otherwise marginal candidate to be considered for listing [6]. Revascularisation of flow limiting lesions has a combined aim of avoiding ischaemia and acute cardiac complications during transplantation, as well as improving longer-term cardiac, patient and graft outcomes beyond 5 years. It unfortunately does not modify the risk of perioperative MI due to plaque rupture, which is more likely with an extensive burden of disease. The potential benefits and limitations of intervention need to be weighed against the risks, including:

- procedural myocardial infarction (of uncertain significance)
- the inherent complications of invasive angiography, including contract induced nephropathy, bleeding complications, dissection or aneurysmal disease; although it is noted that safe performance is well described in LT candidates even with renal dysfunction and bleeding risk [55]
- bleeding risk associated with dual antiplatelet therapy (DAPT)
- delay to transplantation, which can be particularly relevant in patients with cancer or who are rapidly decompensating, who may become a non-viable candidate during the 'stand-down' period on DAPT after revascularisation.

If PCI is performed: Second generation DES are the standard for most PCIs.

Second generation drug eluding stents (DES) are now widely available in New Zealand, with lower stent thrombosis rates compared to earlier generation stents, and a shorter duration of mandatory DAPT. It may be reasonable to re-list a patient for LT after 3 months of DAPT, 1 month in exceptional circumstances.

Patients who have had previous PCI routinely continue aspirin therapy throughout the perioperative period, with close monitoring of platelet counts and bleeding risk while on the waiting list.

The risk continues post-transplantation: Lifelong surveillance and modification of cardiac risk factors is critical

The use of corticosteroids and other immunosuppressants, as well as the development of obesity and non-alcoholic fatty liver disease post-LT, can lead to *de novo* metabolic syndrome, diabetes, hyperlipidaemia, and hypertension, hastening the progression of pre-existing cardiovascular disease. Renal dysfunction is also recognised as contributing to the risk of cardiovascular disease after LT. Close observation and optimisation of cardiac risk should remain a priority post-transplantation to ensure favourable long term outcomes. [56, 57]

Heart Failure and Cardiomyopathy

Mortality from heart failure after LT is estimated to be as high as 15% , with evidence of pulmonary oedema in over 50% of patients in the first post-operative week, being a leading indication for hospital readmission in the first 90-days post-LT [55].

Cirrhotic cardiomyopathy (CCM) is a constellation of cardiac abnormalities found in patients with ESLD, in the absence of known heart disease. It should be considered in the spectrum of heart failure, from being at risk and having structural heart disease, before the development of symptoms or refractory heart failure. Advances in risk assessment and optimisation have been severely limited to date due to the lack of universally accepted diagnostic criteria. The Cirrhotic Cardiomyopathy Consortium proposed updated criteria (cf. the previous 2005 Montreal World Congress of Gastroenterology Criteria) in 2019 (Appendix 3) [58]. The current evidence base indicates CCM is prevalent, affecting up to 50% of patients with ESLD using the Montreal criteria [57[57]. Due to peripheral vasodilation reducing cardiac workload, early cardiac decompensation is often occult in ESLD. With an impaired systolic response to stress, or increases in preload and gradual normalisation of afterload post-transplantation, the risk of heart failure is greatest in the peri- and early post-transplantation period. In the longer term (6-12 months) post-LT the features of CCM are largely thought to reverse [59].

In addition to CCM associated with ESLD, the primary causes of liver failure may also be associated with heart failure, including alcohol abuse, hepatitis C, amyloid disease, and hemochromatosis. The risk of hypertrophic cardiomyopathy is similar to the general population, but inducible LV outflow tract obstruction is also more common in the high-flow state associated with ESLD, a LVOT gradient >36mmHg at peak response during DSE potentially being associated with an increased risk of intraoperative hypotension [60]. Gradients >50 mmHg require a formal cardiology opinion as to the need for further intervention as per current international guidelines, including pharmacotherapy, myectomy, alcohol ablation or pacemaker placement [51]. Systolic and diastolic dysfunction are both broadly recognised as bad prognostic indicators prior to liver transplant, being variably associated with graft failure and mortality, with nil pharmacotherapy proven to modify risk in this specific patient population, and nil consistent thresholds to determine when transplantation is contraindicated [3, 57]. Some experts have recommended an EF <40% is a contraindication to liver transplantation, an EF <50% being a relative contraindication and a threshold for specialist cardiology review [15, 55, 61].

Echocardiography is the primary screening modality, with more advanced strain and doppler measurements featuring in the latest diagnostic criteria for CCM. The addition of exercise/pharmacological stress is useful in certain patients to assess for the absence of contractile or diastolic reserve as a marker of subclinical LV dysfunction in early-stage CCM, and to help predict the potential for decompensation peri-transplantation [58]. Prior to listing for transplantation, specialist cardiology assessment and initiation of heart failure therapies (in liaison with the liver team, as per current international guidelines) should be considered. Moller et al. provide rationale for spironolactone (to counteract the known effects of secondary hyperaldosterism) and a non-selective ß-blocker (to improve the QT interval and reduce the hyperdynamic load), but there is no evidence specific to CCM or other causes of heart failure in ESLD that can currently substantiate this. Close monitoring and early supportive therapy is required in the months post-transplantation when heart failure is one of the most common cardiac complications.

Portopulmonary Hypertension

Portopulmonary hypertension (PoPH) affects around 5-10% of patients with portal hypertension, and is not associated with the presence of cirrhosis or severity of portal hypertension [62]. Hemodynamic criteria include:

1. Mean pulmonary arterial pressure (mPAP) >25 mmHg
2. Pulmonary vascular resistance (PVR) >240 dynes.sec.cm^{-5}
3. Pulmonary arterial occlusion pressure (PAOP) ≤15mmHg

Having met these criteria, the severity of disease is defined as follows:

Severe, mPAP ≥45mmHg
Moderate, mPAP ≥35 to <45 mmHg
Mild, mPAP >25 to <35 mmHg

The International Liver Transplant Society (ILTS) published practice guidelines in 2016 [63]. Those patients with an elevated RVSP on resting echocardiogram, RV impairment or dilatation in the absence of left heart disease, or significant tricuspid regurgitation, should be referred for a right heart catheterisation study to accurately assess pulmonary pressures. The optimal threshold of RVSP between 30-50mmHg is controversial, and ultimately requires a compromise between sensitivity and specificity [7, 62, 64, 65]. The NZLTU currently uses a RVSP threshold of >45 mmHg, as per the AASLD guidelines [7]. One study has shown that patients can develop disease within 2.5-5months [66], and 3 monthly TTE is recommended for comprehensive assessment [65].

The development of PoPH is associated with significant morbidity and mortality, and diagnosis pre-transplantation is important in order to optimise care or prevent futile transplantation. Liver transplantation maybe curative, but transplantation in the context of severe disease is associated with prohibitively high peri- and post-transplantation mortality. In those with moderate-severe disease a trial of pulmonary vasodilator therapy is recommended [7], with reassessment after 3months, in an attempt to reduce mPAP (ideally <35 mmHg) as a bridge to transplantation if RV function is preserved .

Hepatopulmonary Syndrome

Hepatopulmonary syndrome associated with hypoxaemia is diagnosed in 5-30% of adult liver transplant candidates. The International Liver Transplant Society (ILTS) published practice guidelines in 2016 [63]. It should be screened for on pulse oximetry (saturation <96% at sea level) and an arterial blood gas (sitting at room air, P_aO_2 <70 mmHg, Aa gradient >15 mmHg or >20 mmHg if ≥65years). If suspected, a microbubble transthoracic echocardiography should be completed, in conjunction with assessment for alternative causes of arterial deoxygenation on CXR/CT chest and pulmonary function tests.

LT offers a survival benefit, and diagnosis should expedite transplantation with MELD exception points if P_aO_2 <60 mmHg. Once diagnosed, severity should be monitored 3-6 monthly, and oxygen therapy is indicated once P_aO_2 <60 mmHg. Severe disease is likely to prolong recovery post-LT, but eventual resolution of disease is expected 6-12 months post-operatively. [7, 62, 64, 65]

Cardiac Dysrhythmias

The impact of pre-existing dysthymias on LT outcomes is uncertain, and difficult to dissociate from other underlying cardiac pathology in observational studies.

Atrial fibrillation (AF) is the most commonly encountered tachyarrhythmia. It is associated with an increased risk of intraoperative cardiac events and post-transplant cardiovascular morbidity, but variably impacts graft and patient survival [1, 67]. Diagnosis during liver transplantation assessment should prompt consultation with a cardiac specialist, to assess for other cardiac pathology, advise optimal rate control therapy, and rationalise thromboembolic prophylaxis in consultation with the liver team.

Long QT syndrome (QTc >450ms in males, >470ms in females) is prevalent in ESLD patients. In patients with a strong family history or diagnosis pre-dating liver failure, a cardiology referral to consider an implantable defibrillator is required due to the risk of sudden cardiac death. While long QT secondary to liver disease has not been shown to have this association, non-selective ß-blockade is indicated due to the increased risk of post-transplant cardiac events and mortality.

Valvular Heart Disease

Aortic stenosis is particularly concerning in patients undergoing liver transplantation, due to the potential for operative conditions to precipitate ischaemia, life threatening arrythmias and acute decompensation. In light of the high cardiac output state associated with liver failure, assessment of the severity of disease on the basis of the peak velocity and mean gradient can be difficult, with a greater dependence on the valve area to categorise the severity of disease. However, even in asymptomatic patients, borderline 'moderate' disease with a non-reassuring non-invasive stress test may require consideration for transcatheter aortic valve implantation (TAVI) or surgical aortic valve replacement.

In the limited data available, patients with Child-Pugh A ESLD have a mortality risk post-TAVI similar to a non-cirrhotic, while those with Child-Pugh B and C disease, new-onset or chronic AF, or renal impairment are at

much higher risk. While low contrast loads are possible, there is a risk of mild renal injury post-TAVI that may be significant in a candidate with borderline renal function if it impacts their subsequent suitability for liver transplantation [68, 69]. One month of DAPT post-procedure is required, and the implications of delay to transplantation also need to be considered.

Cardiovascular Contraindications to Liver Transplant Surgery

Absolute contraindication [55, 61]:

- Non-revascularized severe obstructive multivessel CAD
- Symptomatic CAD, despite revascularisation
- Left ventricular impairment with ejection fraction <40%
- Moderate-severe right heart failure
- Severe pulmonary hypertension, or moderate pulmonary hypertension with right ventricular impairment, or untreated moderate pulmonary hypertension
- Recurrent ventricular arrythmias
- Severe cardiac valvular pathology
- Aortic stenosis with significant pressure gradients and poor ventricular function

Relative contraindication [55]:

- Non-revascularised moderate obstructive CAD, not involving left main stem or proximal left anterior descending artery.
- Left ventricular impairment with ejection fraction <50%
- Hypertrophic cardiomyopathy with resting left ventricular outflow tract obstruction
- Treated moderate pulmonary hypertension, not responsive to treatment, with preserved right ventricular function
- Recurrent unstable arrythmias

In terms of relative contraindications, other factors such as global cardiac function, risk of surgically difficult transplantation, risk of other organ failure post-transplantation (namely renal), and alternative options to transplantation should be considered in a multidisciplinary forum.

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Appendix

Cardiac Evaluation in NZLTU Liver Transplant Candidates

All liver transplant candidates will have:

12-lead ECG (yearly)
Resting transthoracic echocardiogram (yearly#)
6-minute walk test
TroponinT and NT-pro-BNP
ABG on room air, patient sitting

Portopulmonary hypertension:

If RVSP >35 mmHg repeat resting echocardiogram 6-monthly.

Refer for RHC if RVSP>45 mmHg on resting echocardiogram or RV abnormality (dilatation, impairment), or no RVSP estimate in context of any portal hypertension.

Refer for treatment and repeat RHC as per international guidelines.

Hepatopulmonary syndrome:

Saturation <96% (at sea level) or arterial blood gas (sitting at room air, P_aO_2 <70 mmHg, Aa gradient >15 mmHg or >20 mmHg if ≥65years

Refer for microbubble transthoracic echocardiogram, as per international guidelines.

Valve disease:

As per international guidelines, in consultation with cardiology/cardiosurgical conference.

Consider stress testing to assess significance of moderate-severe disease

Dysrhythmia:

Cardiology assessment for underlying cardiac pathology and medical optimisation, as per international guidelines

Known CAD[ø]

Yes → **Coronary Angiogram**

Repeat if recent PCI/CABG or high risk disease, 12-months if intermediate disease, 24-months if mild disease.

Discuss suitability for treating high risk disease prior, to try and avoid need for a repeat study.

No → **Risk Factors for CAD***

Score >8 → Coronary Angiogram

Score 2-4 → **Positive non-invasive Coronary Investigation:**

CTCA: >50% stenosis

If eGFR <60ml/min or Cr >130 umol/L consider 2nd line:
or **CCS:** >100 AU
(+/- unable to lie flat, breath hold, or AF/tachycardia)
or **ESE/DSE**: induced ischemia or equivocal[¤]

Yes → Coronary Angiogram

No → **Acceptable for listing from a cardiac perspective**

Coronary Angiogram → **Normal or Mild CAD[§]** → **Acceptable for listing from a cardiac perspective**

Coronary Angiogram → **Intermediate CAD[§]** → **Positive non-invasive Functional Assessment:**

ESE/DSE: induced ischemia or equivocal[¤]
or **FFR** <0.8 (or non-hyperemic index <0.93)

Yes → **Multidisciplinary Case Conference:** Otherwise appropriate for transplantation?

Yes → **PCI** with 2nd generation DES and 3/12 DAPT[¥]

or **CABG** in consultation with cardiology/cardiosurgical conference.

Treatment failure[‡] → **Unfit for listing**

No → **Unfit for listing**

No → **Acceptable for listing from a cardiac perspective**

Coronary Angiogram → **High risk CAD[§]** → Multidisciplinary Case Conference

Coronary Angiogram → **Diffuse or untreatable multi-vessel CAD[§]** → **Unfit for listing**

No → **Acceptable for listing from a cardiac perspective**

Cirrhotic Cardiomyopathy or Heart Failure

Cardiology assessment for underlying cardiac pathology and medical optimisation, as per international guidelines

Optimal medical management:

For all patients with any degree of CAD or heart failure**

[#] **Repeat testing while on the transplant waiting list:** For yearly ECG and resting echocardiogram, unless:
<45yr with cholestatic disease, then for two yearly resting echocardiogram
or if RVSP >35 mmHg or mild-moderate valve disease not requiring intervention prior to listing, then for at least 6-monthly resting echocardiogram
or if new symptoms/signs potentially related to cardiac disease/decompensation

[ø] **Known CAD:** any degree of CAD documented on previous invasive or CT angiogram

*** Risk Factors [4, 15, 20, 30] (Mandell 2008, ASSLD, CCS/AHA):**

	Score
Peripheral vascular disease	2
Age >60yrs (or Maori >50yrs)	2
Age 50-60yrs	1
Abnormal LV function (EF<60%, RWMAs, LV hypertrophy)	2
Atrial fibrillation	1
Diabetes Mellitus	2
NASH or obesity (BMI >30kg/m^2 within the last 5years)	2
Current, or >20 PYHx ex-smoker	2
Ex-smoker	1
eGFR <45ml/min	1
Hypertension (or treated)	1
Dyslipidaemia (or treated)	1
Family history (coronary heart disease or sudden cardiac death in a first degree relative male <55yrs old, or female <65yrs old)	1

[¤] **Equivocal ESE or DSE:** Patients unable to achieve a sufficient stress induced workload. A sufficient stress is indicated by:

- >80% maximum predicted heart rate (MPHR) and rate-pressure product (peak HR x peak SBP) > 18,000
- >8METs and stress lasting at least 5 minutes

Induced ischaemia: Any evidence of ischaemia warrants further invasive quantification of the burden of CAD. Whether a patient would be deemed fit with one or two segments of ischemia on stress testing would be determined on a case-by-case basis.

[§] **Classification of CAD:**
High risk CAD defined as >50% LMS or proximal LAD; >90% or 50-90% stenosis with FFR<0.8 major vessel disease
Mild CAD defined as <50% stenosis in left anterior descending, circumflex or right coronary artery (i.e. major epicardial vessels)

[¥] **DAPT after PCI:** Consider risk-benefit for ultra-short 1 month DAPT in conjunction with cardiology and multidisciplinary team (i.e. in stent thrombosis vs risk of bleeding complications, decompensation of cirrhosis or progression of malignancy)

[‡] **Treatment failure**: Revascularisation therapy abandoned, ischaemic symptoms, persistent inducible ischaemia on stress testing, significant troponaemia. All patients who have been revascularized will have monthly troponins, a significant trend or absolute value will be determined on a patient-by-patient basis in consultation with cardiology. Stress testing after revascularisation is only indicated if it was previously positive for occlusive disease.

**** Optimal Medical Management (in consultation with the leading hepatologist and cardiology):** All candidates should be reviewed for suitability of medical optimisation as per current guidelines (including a statin, ß-blocker, +/- calcium channel blocker, and consideration of ACE-inhibitor or ARB) if they have a known history of coronary artery, peripheral vascular disease, or a new diagnosis coronary disease on CTCA, or evidence of heart failure. Current indications for an ACE-inhibitor or ARB include: impaired EF (in ESLD consider <60%), diabetes, hypertension, or eGFR <45 ml/min.

For those acutely or remotely treated with coronary revascularisation, aspirin can be continued at the time of listing and transplantation unless there are significant concerns about the risk of bleeding, or once platelets are $<50 \times 10^9$/L. The type and duration of DAPT after PCI should be decided in conjunction with the treating cardiologist, considering the risk for clopidogrel resistance, the ability to safety reduce the duration of DAPT to three months with newer second generation DES, or an ultra-short one month when there are concerns about bleeding or the risk of decompensation.

Smoking cessation is required for eligibility for listing [7]. Optimisation of diet and exercise, with a focus on maintaining muscle mass, is attended for all patients in the physiotherapy and nutritional listing assessment.

Cardiac Evaluation of Coronary Artery Disease in Liver Transplant Candidates

All liver transplant candidates will have:

12-lead ECG (yearly)
Resting transthoracic echocardiogram (yearly#)
6-minute walk test
TroponinT and NT-pro-BNP (yearly)
ABG on room air, patient sitting

Risk factors:

	Score
Peripheral vascular disease	2
Age >60yrs (or Maori >50yrs)	2
Age 50-60yrs	1
Abnormal LV function (EF<60%, RWMAs, LV hypertrophy)	2
Atrial fibrillation	1
Diabetes Mellitus	2
NASH or obesity (BMI >30kg/m^2 within the last 5years)	2
Current, or >20 PYHx ex-smoker	2
Ex-smoker	1
eGFR <45ml/min	1
Hypertension (or treated)	1
Dyslipidaemia (or treated)	1
Family history	1

Diffuse multi-vessel obstructive CAD

High risk CAD = >50% LMS or proximal LAD; >90% or 50-90% stenosis with FFR<0.8 major vessel disease

Mild CAD = <50% stenosis in left anterior descending, circumflex or right coronary artery (i.e. major vessels)

Known CAD^{ø} — Yes → **Coronary Angiogram**

Repeat if recent PCI/CABG or high risk disease, 12-months if intermediate disease, 24-months if mild disease.

Discuss suitability for treating high risk disease prior, to try and avoid need for a repeat study.

Known CAD^{ø} — No → **Risk Factors for CAD***

Score >8 → Yes → **Positive non-invasive Coronary Investigation:**

CTCA: >50% stenosis

If eGFR <60ml/min or Cr >130 umol/L consider 2nd line:
or **CCS:** >100 AU
(+/- unable to lie flat, breath hold, or AF/tachycardia)
or **ESE/DSE**: induced ischemia or equivocal$^{¤}$

Score 2-4 → **Positive non-invasive Functional Assessment:**

ESE/DSE: induced ischemia or equivocal$^{¤}$
or **FFR** <0.8 (or non-hyperemic index <0.93)

Yes → **Multidisciplinary Case Conference:** Otherwise appropriate for transplantation?

No → **Unfit for listing**

Yes → **PCI** with 2nd generation DES and 3/12 DAPT$^{¥}$

or **CABG** in consultation with cardiology/cardiosurgical conference.

Treatment failure‡ → **Unfit for listing**

No → **Acceptable for listing from a cardiac perspective**

Score ≤1 → **Acceptable for listing from a cardiac perspective**

Normal or Mild CAD§ → No → **Acceptable for listing from a cardiac perspective**

Intermediate CAD§ → Positive non-invasive Functional Assessment

High risk CAD§ → Multidisciplinary Case Conference

Diffuse or untreatable multi-vessel CAD§ → **Unfit for listing**

For all patients with any degree of CAD, optimal medical management:

Statin, ß-blocker or CCB
± ACE inhibitor (if EF<40%, diabetes, hypertension, eGFR <45 ml/min)
± Aspirin (if previous PCI/CABG)

Appendix 3 - Summary of evidence for stress testing and risk assessment in liver transplantation

Dobutamine Stress Echocardiogram

	n	Non-diagnostic test	Sensitivity	PPV	Specificity	NPV
Donovan 1996 [70]	18 + Angio		75%	33%	57%	89%
Plotkin 1998 [71]	40 + Angio +/or Tx		100%	100%	100%	100%
Williams 2000 [72]	121 total, 61 + Angio	55%	0%	0%	91%	80%
Harinstein 2008 [73]	91 + Angio	30%	13%	22%	85%	75%
Patel 2011 [74]	65 EtOH + Angio 140 Non + Angio		33% 64%	9% 23%	84% 61%	96% 90%
Snipelisky 2014 [75]	66 + Angio + Tx	5%	41%	40%	47%	48%
Findlay 2005 [76]	73 + Tx	19%	20%	25%	91%	88%
Umphrey 2008 [40]	157 + Tx	37%				93%
Safadi 2009 [77]	356 + Tx		14%	27%	95%	89%
Nicolau-Raducu 2015 [41]	278 + Tx	30%	9%	33%	98%	89%
Doytchinova 2019 [39]	633 + Angio	24%	24%	23%	90%	90%

Analyses of DSE studies excludes non-diagnostic tests. Abbreviations: n, sample size; Angio, control diagnosis of CAD with angiogram; Tx, control diagnosis of CAD based on cardiac complications during or after transplantation; EtOH, alcoholic liver disease; Non, causes of end stage liver failure excluding alcoholic liver disease.

Nuclear Myocardial Perfusion Imaging

	n	Sensitivity	PPV	Specificity	NPV
Davidson 2002 [78]	83 + Angio	37%	23%	63%	77%
Bhutani 2013 [79]	293 Aden+Angio+Tx 180 Reg+Angio+Tx	54% 35%	32% 27%	82% 88%	92% 91%
Kryzhanovski 1997 [80]	63 + Tx			87%	
Zoghbi 2003 [81]	87 + Tx				99%
Aydinalp 2009 [82]	93 + Tx	100%	15%	61%	100%
Nicolau-Raducu 2015 [41]	47 + Tx	57%	28%	75%	91%

Abbreviations: n, sample size; Angio, control diagnosis of CAD with angiogram; Tx, control diagnosis of CAD based on cardiac complications during or after transplantation; Aden, adensosine; Reg, regadenoson;

Cardiopulmonary Exercise Testing

	Center	n (% test complete)	Transplant rate	Outcome
Epstein 2004 [83]	New England Medical Centre, Boston, USA	156	59 transplanted mean 15m post CPET 6 died (100d)	Peak VO_2 <60% pred & AT <50% pred independently associated with 100d mortality
Dharancy 2008 [84]	Lille, France	149 (91%)	47 transplanted 6 died (1y)	Peak VO_2 <60% pred associated with longer need for oxygen support & lower 1y survival post-tx
Prentis 2012 [85]	Freeman Hospital, Newcastle, UK	182 (91%)	60 transplanted 6 died (90d)	Higher mean AT in survivors (12.0±2.4 vs 8.4±1.3 ml/min/kg, p<0.001) Sensitivity 90.7%, Specificity 83.3%, ROC area = 0.92 (95% CI 0.82-0.97) Optimal AT for survival >9ml/min/kg; AT >11ml/min/kg associated with shorter ICU LOS
Galant 2013 [86]	Brazi	27 (alcoholic cirrhosis)		Higher survival in patients with VO_2 max >14ml/kg/min OR 3.29, (95%CI 1.44-5.25, p<0.0001)
Bernal 2014 [87]	King's College, London, UK	399	223 transplanted median 136d after CPET 4 (90d), 11 (1y) died	Higher median AT in survivors post-tx (11.7 vs 9.8ml/min/kg, p=0.04) AT predictive of LOS & survival before and after transplant
Ow 2014 [88]	South West Liver Unit Liverpool, UK	176 (99%)	PRE-TX: 164 still on WL 90d after CPET (10 died, 2 tx) POST-TX: 57 transplanted mean 25m post CPET	PRE-TX: Higher mean peak VO_2 in survivors without tx, 90d after CPET (21.2±5.3 vs 15.2±3.3ml/min/kg, p<0.001) Sensitivity 90%, Specificity 74%, ROC area = 0.84 (95% CI 0.76-0.92); Optimal peak VO_2 for survival ≥17.6ml/min/kg (PPV 0.18.,NPV 0.99) POST-TX: Peak VO_2 ≥17.6ml/min/kg had better 1 and 2yr post-tx survival

Abbreviations: pred, predicted; tx, transplant; ROC, receiver operating curve; ICU LOS, intensive care unit length of stay; OR, odds ratio; WL, waiting list; PPV/NPV, positive/negative predictive value.

Predictive Models for Early Cardiovascular Outcomes post-Liver Transplantation (from Konerman et al., supplementary materials [4])

Study	Outcome assessed	Outcome timeframe	Model	AUROC
Joeffeson 2014	• Arrhythmia: AF, Aflutter, severe bradycardia, VT, VF • Acute coronary syndrome: "attending cardiologist diagnosis" or ICD-10 code • Sudden cardiac death/acute circulatory failure	3 months 12 months	• Prolonged QTc • Renal impairment • Age >52 years	0.75 0.73
VanWagner 2014	• Cardiac death: cardiac arrest, MI, CHF, arrhythmia, CVA, thromboembolism	30 days	• Age • Gender • Hospitalisation status • ICU status • Ventilator status • MELD • PVT • Local/regional organ sharing • Donor BMI • Cold ischemia time • Transplant center volume (tertile)	0.66
VanWagner 2014	• MI • CHF • AF • Cardiac arrest • CVA • PE	30 days	• Age • MELD • Race • CHF • CVA	0.73
Umphrey 2008	• MI • CHF • Cardiac death • Asystole or symptomatic VT	<4 months post LT	• Maximum achieved heart rate on DSE (MAHR) • MELD • 3.79 + 0.07 MELD – 0.05 MAHR	NR

AF, atrial fibrillation; Aflutter, atrial flutter; BMI, body mass index; CHF, congestive heart failure; CVA, cerebrovascular accident; DSE, dobutamine stress echocardiogram; LT, liver transplantation; TTE, transthoracic echocardiogram; ICU, intensive care unit; MELD, model for end stage liver disease; MI, myocardial infarction; PE, pulmonary embolism; PVT, portal vein thrombosis; VF, ventricular fibrillation; VT, ventricular tachycardia.

Appendix 4 – Diagnostic Criteria Cirrhotic Cardiomyopathy (from Izzy et al. [58])

Proposed criteria by the Cirrhotic Cardiomyopathy Consortium (2019)

Systolic Dysfunction Any of the following:	**Advanced Diastolic Dysfunction** ≥3 of the following:	Areas requiring further validation
• LV ejection fraction ≤50% • Absolute* GLS <18% or >22%	• Septal e' velocity <7cm/second • E/e' ratio ≥15 • LAVI >34 mL/m^2 • TR velocity > 2.8 m/second‡	• Abnormal chronotropic or inotropic response§ • Electrocardiographic changes • Electromechanical uncoupling • Myocardial mass change • Serum biomarkers • Chamber enlargement • CMRI||

e', early diastolic mitral annular velocity.
* GLS is reported as a negative value in echocardiography reports. Changes should be described as changes in the absolute value.
‡ In the absence of evidence of primary pulmonary hypertension or portopulmonary hypertension.
§ Examples include absence of or blunted contractile (e.g. failure to augment ejection by >5% in response to stress; however there is no agreed universal definition) or diastolic reserve on exercise stress testing, dobutamine stress testing, or at rest on CMRI.
|| Myocardial extracellular volume as a surrogate for myocardial fibrosis can be assessed using this modality.

World Congress of Gastroenterology Criteria (2005)

Systolic Dysfunction Any of the following:	**Diastolic Dysfunction** Any of the following:	**Supportive Criteria**
• Blunted contractile response on stress testing • LV ejection fraction <55%	• Deceleration time >200 milliseconds • Isovolumetric relaxation time >80 milliseconds • E/A <1	• Electrophysiological abnormalities • Abnormal chronotropic response • Electromechanical uncoupling • Prolonged QTc interval • Enlarged left atrium • Increased myocardial mass • Increased BNP • Increased proBNP • Increased troponin I