Cardiovascular disease in liver transplant candidates

By

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Thesis
Submitted to Flinders University
for the degree of

Masters of Science by Research

Date of submission: 27th February 2024

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Declaration

I certify that this thesis:

1. does not incorporate without acknowledgement any material previously submitted for a degree or diploma in any university and
2. the research within will not be submitted for any other future degree or diploma without the permission of Flinders University and
3. to the best of my knowledge and belief, does not contain any material previously published or written by another person except where due reference is made in the text

Fadak A Mohammadi
15/10/23

Acknowledgements

I would like to acknowledge the support of my principal supervisor Dr Jeyamani Ramachandran for the guidance in pursuing this idea and the support and expertise to bring it to fruition.

I would like to acknowledge the supports of the associate supervisors – RW, KM and AW other transplant hepatologists at Flinders Medical Centre who taught me the basics of academia in order to complete this thesis.

Dr Sumudu Narayana was employed to assist in the copy editing of the manuscript draft, and her work was greatly appreciated.

I would like to thank my husband Ali, and son Hussain, in addition to my extended family who supported me through the struggles of thesis writing.

Publications during this HDR candidature

Mohammadi, F, Ramachandran, J, Woodman, R, et al. Impact of cardiac dysfunction on morbidity and mortality in liver transplant candidates. Clin Transplant. 2022;e14682. https://doi.org/10.1111/ctr.14682

Presentations during this HDR candidature

Oral presentations

1. Cirrhotic cardiomyopathy, Flinders Medical Centre Gastroenterology Academic Meeting, March 2021
2. Cardiac dysfunction in liver transplant candidates, South Australian Liver Transplant Unit Meeting, Adelaide, July 2021
3. Cardiac dysfunction in liver transplant candidates, *Adelaide Liver Group,* Adelaide, November 2021
4. Coronary artery disease workup in liver transplant candidates, South Australian Liver Transplant Unit Meeting, Adelaide, October 2022

Poster Presentations

1. Impact of cardiac dysfunction on morbidity and mortality in liver transplant candidates, *American Association for the Study of Liver Diseases, Anaheim,* November 2021 (online)
2. Impact of cardiac dysfunction on morbidity and mortality in liver transplant candidates, *Australian Gastroenterology Week, Sydney,* September 2021 (online)
3. Is advanced liver cirrhosis a state of inotropic incompetence?, *Australian Gastroenterology Week, Sydney,* September 2021 (online)
4. A prospective study of global myocardial function in decompensated cirrhosis using advanced echocardiographic techniques and its clinical significance, ILC 2022 (online)

List of Abbreviations

AASLD	American Association for the Study of Liver Diseases
ACCF	American college of cardiology
ACE	Angiotensin converting enzyme
ACLF	Acute on chronic liver failure
AF	Atrial fibrillation
AHA	American heart association
AKI	Acute kidney injury
ARB	Angiotensin receptor blocker
ASE	American Society of Echocardiography
ATN	Acute tubular necrosis
aHR	Adjusted hazard ratio
aOR	Adjusted odds ratio
ANZDATA	Australia and New Zealand Dialysis and Transplant Registry
ANZLTR	Australian and New Zealand Liver Transplant Registry
BMI	Body mass index
BNP	Brain natriuretic peptide
BP	Blood pressure
CAD	Coronary artery disease
cAMP	Cyclic adenosine monophosphate
cGMP	Cyclic guanosine monophosphate
CNI	Calcineurin inhibitor
CO	Cardiac output

COm	Carbon Monoxide
CPET	Cardiopulmonary exercise testing
CVD	Cardiovascular disease
CKD	Chronic kidney disease
CCM	Cirrhotic cardiomyopathy
CT	Computed tomography
CTCA	Computed tomography coronary angiogram
CI	Confidence interval
CA	Coronary angiography
CABG	Coronary artery bypass grafting
DAPT	Dual antiplatelet therapy
DM	Diabetes Mellitus
DD	Diastolic dysfunction
DSE	Dobutamine stress echocardiography
E/A ratio	Early diastolic atrial filling ratio
ECG	Electrocardiogram
EDV	End diastolic volume
EF	Ejection fraction
ESLD	End-stage liver disease
ePAP	Estimation of pulmonary artery pressure
FFR	Fractional flow reserve
GFR	Glomerular filtration rate
GLP-1	Glucagon like peptide 1
GLS	Global longitudinal strain

HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
HT	Hypertension
HR	Heart rate
HPS	Hepatopulmonary syndrome
HRS	Hepatorenal syndrome
IL1β	Interleukin 1β
ICD	International classification of diseases
INR	International normalised ratio
IQR	Interquartile range
KDIGO	Kidney Disease Improving Global Outcomes
LGE	Late gadolinium enhancement
LA	Left atrium
LAVI	Left atrial volume index
LDL	Low density lipoprotein
LVAD	Left ventricular assist devices
LV	Left ventricular
LVEDP	Left ventricular end diastolic pressure
LVEF	Left ventricular ejection fraction
LT	Liver transplant
MACE	Major adverse cardiac events
MRI	Magnetic resonance imaging
mPAP	Mean Pulmonary artery pressure
MET	Metabolic equivalent of tasks

MELD	Model of end-stage liver disease
MI	Myocardial infarction
NO	Nitric oxide
NOS	Nitric oxide synthetase
NALFD	Non-alcoholic fatty liver disease
NF-κB	Nuclear factor kappa beta
PAMP	Pathogen-associated molecular patterns
PCI	Percutaneous coronary intervention
PPHTN	Porto-pulmonary hypertension
PET	Positron emission tomography
PVR	Pulmonary vascular resistance
RA	Refractory ascites
RV	Right ventricle
RVSP	Right ventricular systolic pressure
RRT	Renal replacement therapy
SPECT	Single-photon emission computed tomography
SGLT2	Sodium-glucose co-transporter 2
SALTU	South Australian Liver Transplant Unit
SV	Stroke volume
SD	Systolic dysfunction
TIPSS	Trans-jugular intrahepatic portosystemic shunting
TTE	Transthoracic echocardiography
TNF-α	Tumour necrosis factor alpha

Grants and Financial Support: None

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Introduction

Cardiovascular disease (CVD) in liver transplant (LT) candidates is increasingly recognised as a leading cause of morbidity and mortality before and after transplantation (1, 2). Heart failure and significant arrhythmias contribute up to 50% of heart related hospitalisations in the early post-transplant period (3). Over time, the accumulation of cardiac risk factors results in coronary artery disease (CAD) post-transplant (4, 5). The changing demographics of patients being considered for LT, such as older patients, increasing non-alcoholic fatty liver disease (MAFLD), and pre-existing CAD, make cardiac risk an important consideration in LT candidates (6, 7). MAFLD is increasingly recognised for its association with CVD, including the higher risk of CAD and as an independent risk factor for heart failure (8, 9). Cirrhotic cardiomyopathy (CCM) is also an increasingly recognised extra-hepatic complication of cirrhosis. CCM is defined as the presence of systolic and/or diastolic dysfunction (DD) in cirrhotic patients in the absence of other causes of cardiac dysfunction (5). While typically subclinical, it can present as overt cardiac failure under stressors such as LT, use of beta blockers and trans-jugular intrahepatic portosystemic shunting (TIPSS) (10).

The first chapter of this thesis covers the different causes of cardiac dysfunction in cirrhosis and the cardiac considerations in pre-, peri- and post-transplant settings. The second chapter of this thesis highlights the impact of cardiac dysfunction on morbidity and mortality of LT candidates, and the incidence of post-transplant CVD over the past 10 years in the South Australian Liver Transplant Unit (SALTU). The third chapter describes the management and clinical outcomes of LT candidates with pre-existing CAD, including post-transplant CAD, over the past 10 years in the SALTU. The fourth chapter reviews the evidence and changes in cardiac evaluation of LT candidates based on international guidelines and presents a risk factor based diagnostic pathway than can be implemented in SALTU successfully, with the aim of improving management of CVD in LT candidates. Finally,

a summary and recommendations for areas of further investigation will be presented to conclude this thesis.

Chapter 1

Literature review of cardiovascular diseases in liver cirrhosis

1.1 Systemic haemodynamic changes in cirrhosis

The presence of clinically significant portal hypertension is a hallmark of decompensated cirrhosis and is a predictor of poor prognosis (11). According to Ohm's law the change in pressure across the portal system (ΔP) is directly proportional to blood flow (Q) in the portal system and resistance, which mathematically is expressed as $\Delta P = Q \times R$ (12). In decompensated cirrhosis, the severely fibrosed liver causes increased resistance (R) to blood flow (12). The increased resistance mediates increased release of vasoactive mediators including adrenomedullin, calcitonin, carbon monoxide, endocannabinoids and nitric oxide; while degradation of these vasoactive mediators is impaired as the decompensated liver is unable to metabolise them (13). Through angiogenesis, porto-systemic collaterals are formed, segmenting blood flow (Q) in the portal system. With increasing Q and R, there is an increase in pressure across the portal system resulting in the clinical complications of portal hypertension including ascites, hydrothorax and variceal bleeding (12). Due to the vasodilatory effects of mediators, such as NO, on the systemic circulation, there is reduced venous return and a compensatory increase in baseline heart rate to maintain cardiac output (CO). Thus a hyperdynamic circulation ensues in cirrhosis. (14). While there is pooling of blood in the splanchnic circulation the rest of the systemic circulatory system is in a state of relative arterial hypotension. The peripheral receptors of vasoconstriction are downregulated with concomitant RAAS activation in an attempt to improve systemic organ perfusion (15). There is limited physiologic reserve for CO to increase any further in the setting of additional stressors on the cardiovascular system such as exercise, stress or sepsis (15). For patients with pre-existing CVD, the haemodynamic changes of CCM can contribute to multi-organ failure.

1.2 Myocardial changes in cirrhosis

At an intracellular level, active cardiac contraction, or systole, involves activation of myosin heavy chains forming a cross-bridge with thin actin filaments (14). Myosin exists in efficacious alpha units and weaker beta subunits. In the setting of cirrhotic cardiomyopathy, the weaker beta myosin subunit is upregulated (14). Similar abnormalities are seen during the active phase of diastole in other cardiomyopathies (16). At a histologic level, CCM causes myocardial hypertrophy and subendothelial oedema, with eventual progression to fibrosis (17). The earliest phase of fibrosis is diffuse myocardial fibrosis, which is considered reversible, followed by subendothelial segmental fibrosis, which is considered permanent(17). The degree of fibrosis can be quantified using cardiac magnetic resonance imaging (MRI), whereby permanent fibrosis is measured using late gadolinium enhancement. Other observed myocardial changes in cirrhosis include increased left ventricular (LV) mass, increased LV end diastolic volumes, and increased left atrium (LA) volumes (18).

1.3 Causes of cardiac dysfunction in cirrhosis

1.3.1 Coronary Artery Disease

Cirrhosis has previously been considered to be a protective factor against CAD, owing to the lower cholesterol levels, thrombocytopenia, coagulopathy and hyperdynamic circulation (19). However, a recent meta-analysis of obstructive CAD in cirrhosis found the estimated prevalence to be 12.6%, similar to that of the general population (19). Therefore, patients with cirrhosis remain at risk of other complications of CAD including ischaemic cardiomyopathy and arrhythmia. Furthermore, both platelet count and INR have been demonstrated to be inaccurate predictors of coagulation in cirrhosis due to a rebalancing of thrombotic factors that increases the risk of bleeding and clotting in cirrhosis (20). Management of CAD risk factors, including the use of statins for dyslipidaemia, is strongly encouraged, particularly given the complexity of revascularisation in this vulnerable population (21).

CAD has become a prevalent cause of cardiac dysfunction in cirrhosis and hence an appropriate risk assessment is essential prior to LT. Patients with multiple cardiovascular risk factors and/or metabolic syndrome are more likely to benefit from angiographic coronary testing and revascularisation pre-transplant (22). CAD will be covered in further detail in section 1.8.

1.3.2 Metabolic associated fatty liver disease

MAFLDMetabolic associated fatty liver disease (MAFLD) is defined as the presence of hepatic steatosis in addition to DM, obesity, or other evidence of metabolic dysregulation (23). To reflect the changes to nomenclature of fatty liver disease, MAFLD will be used from hereon, acknowledging that the majority of articles reviewed in this thesis refer to the original definition of non-alcoholic fatty liver disease (NAFLD). The incidence of MAFLD has steadily increased, with prevalence rates of up to 30% in developed countries (24, 25). In fact, MAFLD has become the leading aetiology of cirrhosis in LT candidates in the US, superseding other indications (26). A similar rise has been observed by the Australia and New Zealand Liver Transplant Registry (ANZLTR) (27). Increased recognition of MAFLD has resulted in re-diagnosis of cases previously labelled as cryptogenic cirrhosis. Better recognition of MAFLD has highlighted the need for better liver directed therapies for this clinical entity. Currently, the only effective and proven treatment for MAFLD is lifestyle modification including weight loss (8).

A recent systematic review concluded that there is a significant association between MAFLD and CAD (both fatal and non-fatal events) (25). The risk of significant CAD was found to increase as liver fibrosis progresses, independent of the presence of other cardiovascular risk factors (25). In LT candidates with decompensated cirrhosis, features of metabolic syndrome to support a MAFLD diagnosis may be difficult to detect. This is due to dysregulation of the lipid profile and the chronic

catabolic state of cirrhosis masking significant insulin resistance and obesity, and the chronic vasodilatory state manifesting as persistent hypotension (25).

MAFLD is also suggested to be a key driver in cardiac remodelling – a substrate for electrical dysfunction – in addition to diastolic dysfunction and heart failure (8). A retrospective analysis of nearly one million patients with or without MAFLD found that a significantly higher risk of incident heart failure occurred in MAFLD patients, independent of other heart failure risk factors (28). The exact pathophysiologic processes from MAFLD to progressive myocardial dysfunction are not yet defined. Some of the proposed mechanisms include insulin resistance and mitochondrial dysfunction, RAAS activation, systemic inflammation and gut dysbiosis (8). A similarity is seen between these pathophysiologic mechanisms and those in CCM and will be discussed in more detail in section 1.4.

1.3.3 Alcoholic cardiomyopathy

Alcohol induced dilated cardiomyopathy can occur independent of the presence of cirrhosis. However, given the prevalence of alcohol misuse disorder is up to 1 million people, alcoholic cardiomyopathy is likely under-recognised (29, 30). Alcoholic cardiomyopathy may be differentiated from CCM based on a recent history of alcohol excess, prominent ventricular dilatation, a lower EF on echocardiography and clinically more evident heart failure (29). With abstinence from alcohol, the prospects of recovery of ejection fraction (EF) and cardiac function are generally favourable. There is limited evidence for the efficacy of heart failure therapies in alcohol related cardiomyopathy (29). Given the traditional requirement of a minimum of 6 months abstinence for patients prior to LT consideration, it is uncommon to see alcoholic cardiomyopathy persist as an issue for future LT candidates (16).

1.3.4 Amyloidosis induced restrictive cardiomyopathy

Light chain and transthyretin (in both the hereditary and non-hereditary forms) amyloidosis can cause restrictive cardiomyopathy (31). Early diagnosis of amyloidosis is hampered by mild early signs and normal transthoracic echocardiogram (TTE). The overall prognosis in these patients remains poor with estimated survival up to 5 years, despite treatment with chemotherapy for light chain amyloidosis (31). For patients with hereditary transthyretin amyloidosis, LT can be offered given the variant protein is produced by the liver and LT arrests production of the dysfunctional protein (31). Outcomes in the setting of LT and hereditary amyloidosis remain poor, as cardiomyopathy can continue to progress regardless of LT (31).

1.3.5 Haemochromatosis induced cardiomyopathy

Haemochromatosis is highly prevalent in the general population, with up to 30% of the Australian population being carriers for a mutation related to hereditary haemochromatosis (32). Cardiomyopathy is also an irreversible complication of untreated iron overload, both from acquired and hereditary causes (33). Haemochromatosis is associated with an increased risk of cardiovascular mortality, up to 14 times, and this association has also been seen post-transplant (33). Cases of heart failure post-transplant for hereditary haemochromatosis have been described, with successful treatment through regular venesection and heart failure specific therapies (34).

1.4 Cirrhotic Cardiomyopathy

1.4.1 Summary

CCM is an increasingly recognised extra-hepatic complication of cirrhosis. CCM is defined as the presence of systolic and/or diastolic dysfunction in cirrhotic patients in the absence of other causes of cardiac dysfunction, irrespective of the aetiology of cirrhosis (5). While typically subclinical, it

can present as overt cardiac failure under stressors such as liver transplant surgery (LT), use of beta blockers, and TIPSS (10). The pathophysiological mechanisms for worsening of CCM under stress include increased peripheral vasoconstriction under the demands of bleeding, shock, and vasopressors; withdrawal of beta blockers; and reversal of renin-aldosterone-angiotensin-system (RAAS) in the early post-transplant period (35).

1.4.2 Introduction

Decompensated cirrhosis and portal hypertension result in a persistent hyperdynamic circulatory state that pushes the physiologic reserve of the heart (13). There are several key mechanisms that are proposed to contribute to the development of CCM in the setting of portal hypertension including RAAS activation, upregulation of the sympathetic nervous system, downregulation of beta-receptors, and chronic systemic inflammation (13). CCM can occur with cirrhosis of any aetiology, however, a cumulative risk for cardiac dysfunction is seen in alcohol and MAFLD related cirrhosis (33). Therefore, development of CCM should be considered as a potential extra-hepatic complication of portal hypertension. CCM is typically subclinical and is primarily diagnosed by echocardiography. Electrocardiogram (ECG) and serum biomarkers such as brain natriuretic peptide (BNP) and troponin may support the diagnosis but are not diagnostic in isolation for the diagnosis of CCM (16). The most common manifestation of CCM is diastolic dysfunction (DD), with cardiac stress testing revealing inducible systolic dysfunction (SD) (33). The diagnostic criteria, which were proposed in 2005, have since been updated in 2020 to include more sensitive transthoracic echocardiography (TTE) parameters — most importantly to include global longitudinal strain (GLS).

CCM increases the risk of cardiovascular disease, renal morbidity and mortality in LT recipients (15, 36). In addition, there is mounting evidence suggesting that myocardial dysfunction, including the

changes that occur in CCM, may persist in the post-transplant period and contribute to post-transplant CVD (37). Hence, it is important to explore the potential pathophysiologic mechanisms of CCM and the pitfalls in its diagnosis using routine cardiac investigations.

1.4.3 Prevalence of CCM

The prevalence of CCM varies widely based on the diagnostic criteria applied, with a recent comprehensive review reporting prevalence rates of 26–81% (16). Reported factors that hinder accurate estimation of its prevalence include variability in definition of CCM used in these studies; some defining CCM by DD alone (38), use of individual echocardiographic parameters in the definition of DD (39, 40), inclusion of patients with pre-existing CVD, or only measuring clinical heart failure events (41, 42). Prevalence also varies based on the diagnostic criteria used, either the original 2005 World Congress of Gastroenterology criteria or the newly proposed criteria by the CCM Consortium (37). The prevalence of CCM based on CCM Consortium criteria was found to be similar to the original 2005 criteria (55.7% compared to 67.2%), however, a significantly higher proportion of these patient had detected SD (43). Post-mortem cardiac examination revealed that myocardial hypertrophy was significantly more common in cirrhosis compared to age and gender matched controls with a prevalence rate of 24%. This association was higher in those with MAFLD cirrhosis, and less so in cholestatic liver diseases (44). This is in contrast to the current understanding that the incidence of CCM is independent of the aetiology of cirrhosis (16). Despite varying prevalence studies, the incidence of CCM remains closely related to the progression of cirrhosis with other features of portal hypertension (36, 45). Major physical stressors, such as TIPSS or LT, are major precipitants to clinical presentation of CCM. Uniform adoption of the new proposed diagnostic criteria for CCM will facilitate a true estimation of the prevalence of CCM.

1.4.4 Pathophysiology of CCM

Multiple, complex processes are implicated in the pathophysiology of SD and DD that often act in parallel and in combination with each other. These include dysfunction in myocardial receptors, changes in cardiac myocyte plasma membrane fluidity that affect cardiac contractility and relaxation, inflammatory and vasoactive mediators that impair cardiac contractility in addition to worsening cardiac strain and cardiomyocyte apoptosis (46). In addition, RAAS activation also contributes to DD and cardiomyocyte alterations via the direct effect of angiotensin II on myocardial hypertrophy (47).

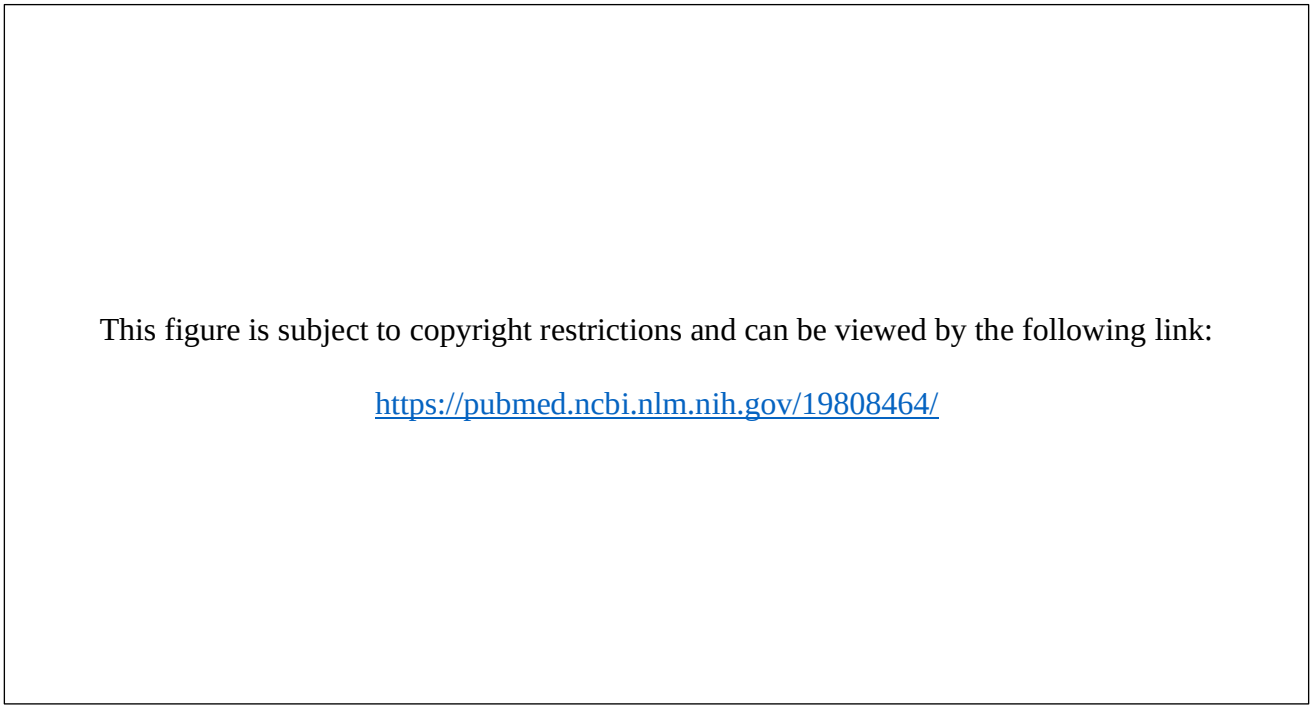

Figure 1.1: Cardiac action potential with flow of ions, reproduced from reference (48)
Membrane currents that generate the a normal action potential. Resting (4), upstroke (0), early repolarization (1), plateau (2), and final repolarization are the 5 phases of the action potential. A decline of potential at the end of phase 3 in pacemaker cells, such as the sinus node, is shown as a broken line. The inward currents, I_{Na} (sodium), I_{Ca} (calcium), and I_K (potassium) are shown in yellow boxes; the sodium-calcium exchanger (NCX) is also shown in yellow. It is electrogenic and may generate inward or outward current (48).

The inward flow of sodium (Na), calcium (Ca) and potassium (K) at specific time intervals is crucial to the propagation of an action potential through the myocardium (Figure 1.1) (48). Depolarisation results in the recruitment of actin and myosin, ultimately resulting in a synchronised myocardial

contraction. The cellular changes that occur in cirrhosis include downregulation of B-adrenoreceptors (49), impaired membrane fluidity (50), and dysfunction of L-type ion channels specifically for calcium and potassium receptors (51). Cardiomyocyte contraction depends on Ca influx entering via L-type channels to activate intracellular muscle mechanisms. The reduced structure and function of L-type Ca channels in patients with CCM is associated with electromechanical uncoupling, impaired myocardial relaxation, and QT prolongation on ECG (52). Electromechanical uncoupling refers to the prolonged delay that occurs between isometric ventricular depolarisation and myocardial contraction to allow ejection of blood from the heart. This phenomenon has been described as more common in cirrhotic patients both at rest and after exertion and forms part of the original diagnostic criteria of CCM (52).

1.4.4.2 Myocardial receptor dysfunction

In the myocardium, beta-1 receptors have a positive inotropic (increase myocardial contractility) and positive chronotropic effect (increased heart rate) (16). This is mediated by the generation of cyclic adenosine monophosphate (cAMP), which phosphorylates the sarcoplasmic reticulum resulting in a calcium surge that mediates muscle contraction (16). In order to produce cAMP, G-proteins at the cell membrane need to be stimulated. Persistent cardiac beta-1 adrenergic receptor signalling is a key pathophysiologic process in CCM (46). The excessive sympathetic nervous system activation eventually leads to down-regulation of the beta-1 receptor, and subsequent impaired inotropic and chronotropic response of cardiac myocardium to sympathetic stimulation (16, 46). Animal studies have been performed where constant sympathetic nervous system activation in mice with portal hypertension correlated with desensitisation and downregulation in beta-1 receptor density (45). This has been observed in association with changes in cardiac myocyte membrane fluidity, which impairs beta-receptors from coupling to G-proteins, and therefore downstream impairment of myocardial

contractility (49). In a vicious cycle, there is further beta-1 receptor stimulation to maintain systemic perfusion, which can lead to overt myocardial dysfunction in the advanced stages of cirrhosis (49).

Clinically, the impaired activation of beta-1 receptors manifests as impaired myocardial response to catecholamines, otherwise known as inotropic incompetence in CCM (16). This is similar to the neurohormonal responses seen in other cardiomyopathies (36). Recently, translational research has been performed to determine the significance of anti-beta-1 adrenergic receptor antibodies in the development of CCM (53) Serum levels of anti-beta-1 receptor antibodies were found to be significantly higher in CCM patients compared to healthy and non-CCM cirrhotic patients (53). Elevated antibody levels also correlated with lower EF and elevated early diastolic atrial filling ratio (E/A ratio) as an early marker of DD (53). Further studies are needed to determine the significance of these antibodies in the development of CCM and their utility as a screening biomarker for CCM.

1.4.4.3 Renin-Aldosterone-Angiotensin-System

In compensated cirrhosis, systemic vasodilation is counterbalanced by an increase in CO. CO is defined by the equation of CO = heart rate (HR) x stroke volume (SV), summarised as CO = HR x SV (54). As cirrhosis and portal hypertension progresses, there is an increase in autonomic activation to increase HR and an increase in contractility to improve SV, as previously described. These factors are limited by age, gender and baseline fitness levels. The hypoperfusion in the systemic circulation results in the intense activation of the RAAS system, resulting in salt and water retention through increased angiotensin II, increased aldosterone, and the activation of the sympathetic nervous system (Figure 1.2). The RAAS system also plays an important role in the development of CCM. Angiotensin II is implicated in left ventricular remodelling, while high aldosterone levels result in profound salt retention, leading to concentric LV hypertrophy. This contributes to the DD seen in CCM (46).

Progressive vasoconstriction – mediated by angiotensin II constricting the efferent arteriole in the nephron – sought to maintain normotension in advanced cirrhosis contributes to renal dysfunction. This state of effective renal hypoperfusion was traditionally thought to be a major contributor to the development of HRS. However, recent studies have highlighted the importance of cardiac dysfunction as an additional major contributor to the development of HRS, and this will be discussed in further detail below.

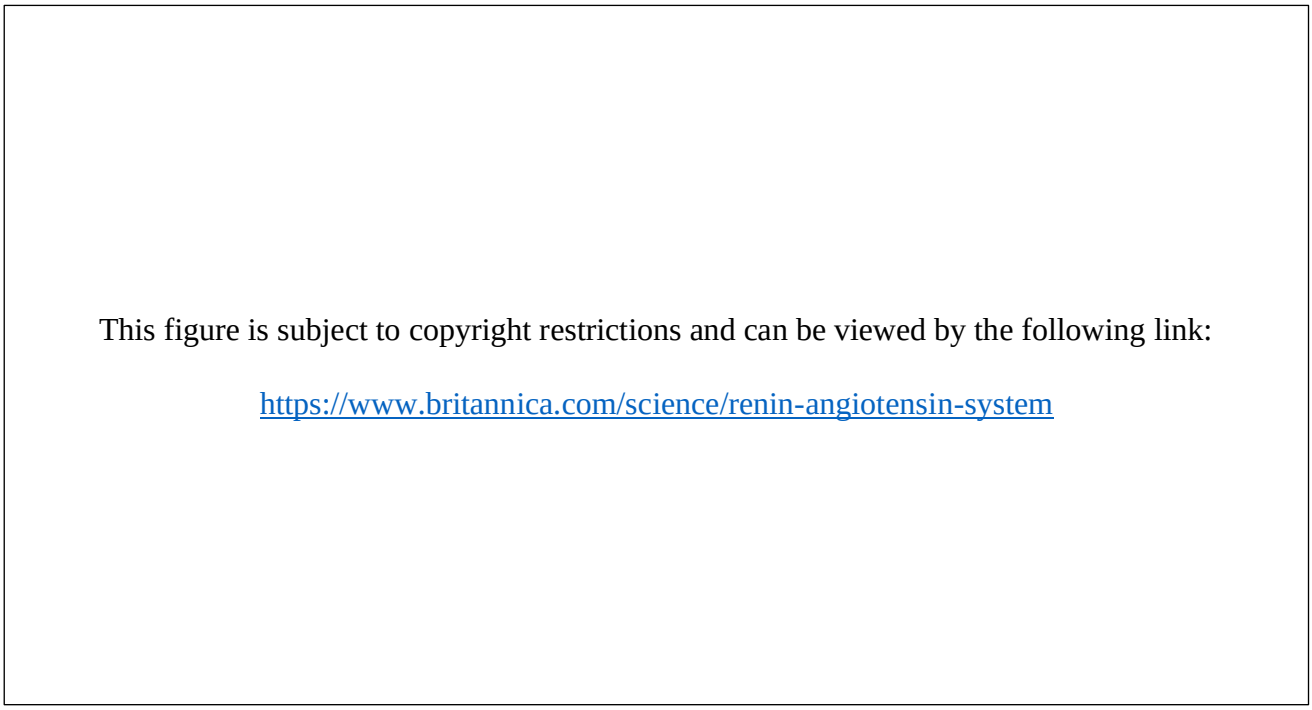

Figure 1.2: The renin-angiotensin system, reproduced from reference (55) NaCl – sodium chloride, H20 – hydrogen dioxide, ACE – angiotension-converting enzyme

1.4.4.4 Molecular mediators of cardiac dysfunction in CCM

Nitrous oxide

The pathogenetic role of NO in cirrhosis has been well-studied. Its negative inotropic effect plays a significant role in contributing to SD noted in CCM. NO is produced by nitric oxide synthetase

(NOS), which has three isoforms (NOS 1, 2 and 3). NO synthesis occurs constitutively, in addition to being induced by systemic inflammation (13, 16). NO is one of the most potent vasodilators involved in regulating vascular tone and contributing to a hyperdynamic circulatory state (15). NOS1 has a direct negative inotropic effect on myocardium. NO exerts its effect by stimulating guanylate cyclase to produce cyclic guanosine monophosphate (cGMP), which phosphorylates G proteins to inhibit calcium influx into the cardiac myocyte (56). NO also has an indirect negative inotropic effect by preventing the activation of beta-1 adrenergic receptors and by inducing apoptosis (13, 16). Due to portal hypertension and the chronic inflammatory state of cirrhosis, plasma NO levels are persistently elevated in cirrhosis which contributes to myocardial dysfunction (57). This is proven by the improvement noted in cardiac contractility upon the administration of NO synthesis inhibitors to cirrhotic rats (57). Thus, normalisation of NO production and elimination has the potential to improve ventricular contractility and correct the systemic haemodynamic abnormalities found in cirrhosis.

Carbon Monoxide

Carbon monoxide (COm) is another evanescent gas that increases the activity of the haemo-oxygenase enzyme, and contributes to splanchnic arterial vasolidation (56). Similar to NO, COm impedes calcium influx into cardiac myocytes by production of cGMP, with resultant reduction of calcium influx to cardiac myocytes (56). Zinc protoporphyrin is an inhibitor of the haemo-oxygenase enzyme, thereby blocking the effects of COm on cardiac contractility (58). In studied ventricles of cirrhotic rats, treatment with zinc protoporphyrin significantly reduction cGMP production, and improved cardiac muscle contractility, supporting the pathogenetic role of COm in CCM (58).

Inflammatory mediators

Inflammatory mediators are commonly encountered in cirrhosis, and are strongly implicated in the pathophysiology of CCM (45). Increased bacterial translocation is one of the most important pathogenic mechanisms responsible for activation of the inflammatory cascade in cirrhosis (15). The dysbiosis characteristic of advanced portal hypertension leads to translocation of pro-inflammatory bacteria into the systemic circulation through ascitic fluid to stimulate the release of cytokines as part of a cytokine "storm" (15). Chronic inflammation from persistent bacterial translocation continues to be a major contributor for progression and complications of cirrhosis (15). These cytokines including tumour necrosis factor alpha (TNF-α), interleukin 1β (IL1β) and nuclear factor kappa beta (NF-κB) are all associated with attenuation in cardiac myocyte contractility and the pathogenesis of CCM (15).

The pathogen-associated molecular patterns (PAMPs) that are expressed on the outer membrane of bacteria are recognised by the innate immune system, triggering release of TNF-α and IL1β (15). TNF-α administration in rodent cirrhotic hearts has been shown to have a dose and time dependent effect on cardiac contractile dysfunction (15). Inhibition of TNF-α using monoclonal antibodies, resulted in the restoration of cardiac contractility in these mice. TNF-α has also been demonstrated to impede calcium homeostasis within muscle cells, further preventing peak cardiomyocyte contraction during systole or active relaxation in diastole (59). IL1β, a cytokine that usually potentiates the inflammatory signal, has also been shown to correlate with depressed cardiac reserve (15). Both TNF-α and IL1β bind to the cell membranes of cardiac myocytes to induce increased synthesis of NO, and thereby attenuation of cardiac contractility (60).

NF-κB is another potent regulator and inducer of pro-inflammatory genes to potentiate cytokine expression; increased NF-κB levels are seen in cirrhosis (61). In cirrhotic rats, increased myocardial levels of NF-κB were demonstrated, and blockade of the NF-κB pathway reduced both NF-κB

activity and TNF-α expression, with subsequent improvement of cardiac contractility (61). Together, these pro-inflammatory mediators directly inhibit cardiac contractility. This negative inotropic effect is particularly unfavourable given that the systemic circulation is already in a persistent hyperdynamic state (62). The adverse effect of inflammatory mediators is responsible for the cardiac and circulatory dysfunction often noted as a part of acute, severe multi-organ dysfunction – in acute on chronic liver failure (ACLF) – that is associated with significant mortality (62).

Endocannabinoids

There are several subtypes of endocannabinoids including arachidonoyl ethanolamine and 2-arachidonoylglyceral (16). They bind to cannabinoid receptors in the heart to reduce myocardial contractility (16), contributing to the cardiovascular alterations in CCM. In addition, endocannabinoid upregulation has been linked to arterial hypotension in cirrhosis (63). A prospective observational study reported that endocannabinoids were upregulated in cirrhosis, and endocannabinoid levels continue to rise in a linear fashion with increasing severity of liver disease, which was measured using the Model for End-stage Liver Disease (MELD) score (64). Blockade of endocannabinoids in rat models resulted in improved cardiac contractility, supporting the important role that these vasoactive mediators play in cardiac dysfunction of CCM (21).

Bile acid

Cardiac myocytes are densely populated with bile acid receptors such as the farnesoid-X activated receptor, the function of which remains unclear (13, 59). Previous *in vitro* studies have previously shown that bile acids act as a direct myocardial toxin by depressing beta-1 receptor activity (36),

resulting in a negative inotropic and chronotropic effect that attenuates cardiac responses to sympathetic activation (65). Other animal studies demonstrated that membrane fluidity and mitochondrial function were also adversely affected in the presence of severe cholestasis, in addition to beta-adrenergic receptor downregulation (65, 66).

Role of apoptosis in CCM

Apoptosis is a key cellular pathway that is controlled by cytokines and transcriptive proteins, including transforming growth factor beta (TGF β) and p38 apoptosis (p38a) (60). These proteins are elevated in the circulation of cirrhotic patients, and have been demonstrated to contribute to ischaemia and cardiac myocyte apoptosis (60). The excess circulating NO in cirrhosis is also implicated in contributing to apoptosis of cardiac cells (60).

1.4.5 Cirrhotic cardiomyopathy and renal dysfunction

The presence of CCM is increasingly considered to be a risk factor for the development of hepatorenal syndrome (HRS) (67). In a longitudinal study of ascites and renal dysfunction, low CO was found to be an independent predictor of developing HRS (67). Another study that evaluated DD in cirrhosis found a positive association between DD and the development of HRS and encephalopathy over a 6-month period.

1.4.5.1 Pathophysiology of HRS in CCM

Haemodynamic interactions in HRS

In the initial stages of cirrhosis there is excess synthesis of vasoactive mediators, which is compensated with development of hyperdynamic circulation (67). With progression of portal

hypertension, there is functional vasoconstriction of other peripheral organs, including the kidneys, to maintain systemic perfusion. This is achieved through excessive sympathetic nervous system activation, accumulation of vasoactive mediators as described above, and intense RAAS activation (67). In the presence of myocardial dysfunction in CCM, there is a lack of response to activation of the systemic nervous system, resulting in progressive decline of left ventricular ejection fraction (LVEF) at the end-stages of liver disease. Diminished cardiac output, arterial hypotension, and excess noradrenaline are often present in the final stages of liver failure (Figure 1.3) (67). At these final stages of liver disease, hepatorenal syndrome (HRS) develops as a consequence of multi-factorial renal hypoperfusion .

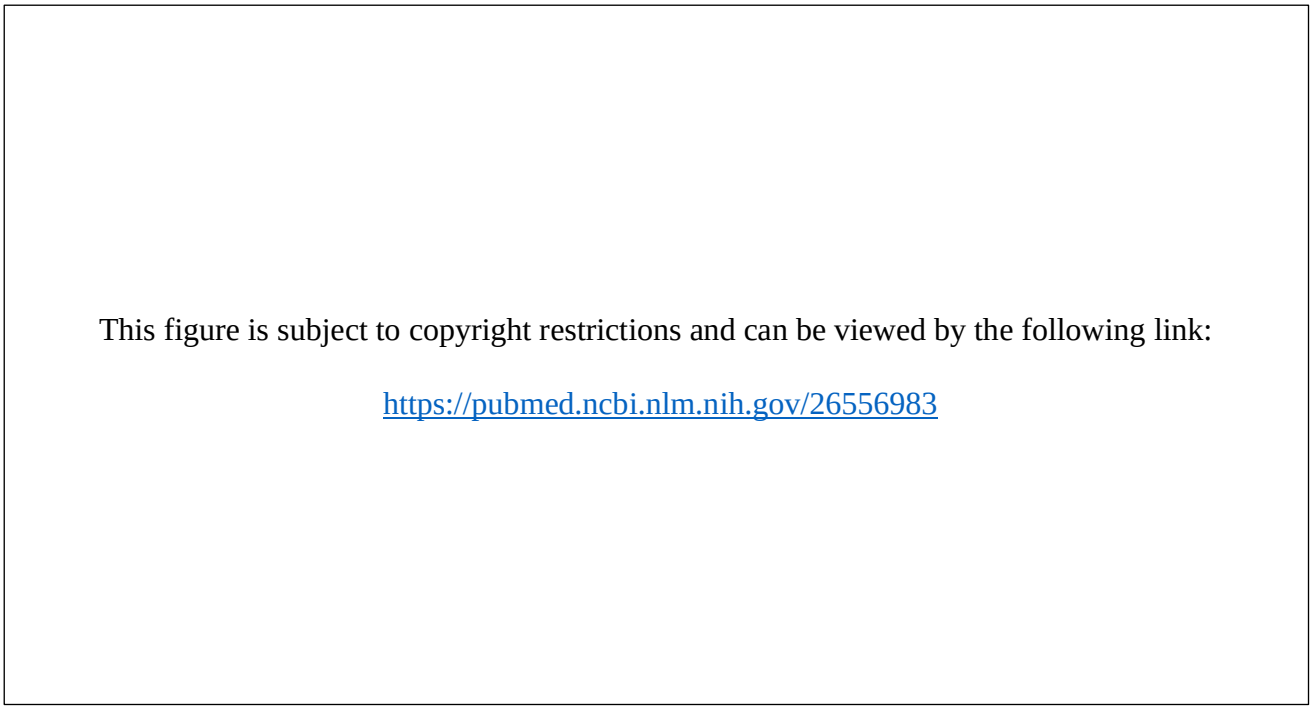

Figure 1.3: Cardiac dysfunction with the progression of decompensated cirrhosis and ascites, reproduced from reference. Initially, circulatory homeostasis is maintained by the development of a hyperdynamic circulation. Later during the course of decompensated cirrhosis, patients develop an activation of the vasoconstrictor systems to maintain arterial pressure. In subsequent stages, the progressive decrease in cardiac afterload is not followed by an increase in HR and CO due to a decrease in cardiac function. Finally, in the advanced phase, when impairment of effective arterial blood volume is extreme, patients showed increased activity of NE concentration, arterial hypotension and reduced LVSF (CO and LV stroke work), and cardiac chronotropic function, and a

higher degree in LVDD (E/e') as compared to those with ascites, but normal NE, or without ascites. E/e'ratio: Peak E-wave transmitral/Peak early diastolic mitral annular velocity. (67)

Other pathophysiologic mechanisms in HRS

HRS is traditionally considered a sequelae of severe portal hypertension, splanchnic vasodilation, and depletion of effective circulating volume (68). The hyperdynamic circulation itself encroaches on cardiac reserve, and at extremes of liver disease, cardiac output falls (69). With loss of renal perfusion comes the development of AKI. Recently, this theory has been challenged. In addition to the haemodynamic changes of end stage cirrhosis, chronic systemic inflammation and release of cytokines are also major contributing factors resulting in microthrombi and direct renal tubular damage in HRS/AKI (69) (Figure 1.4). Similar to the pathophysiology of CCM, chronic systemic inflammation also appears to contribute to HRS, independent of the presence of an acute bacterial infection . The upregulation of the innate immune system and elevated levels of TNF-a, interleukin-6 and C-reactive protein are ubiquitously seen in decompensated cirrhosis (68), and may contribute to both endothelial and cardiovascular dysfunction.

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Figure 1.4: Proposed mechanism for HRS, reproduced from reference (68)
At this advanced stage of cirrhosis, evidence shows that there is a decrease in cardiac output, which may also contribute to the decrease in effective arterial blood volume. There is growing evidence suggesting that systemic inflammation also plays an important role in the pathophysiology of HRS. It is hypothesized that pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) deriving from bacterial translocation and from injured liver, respectively, may activate circulating innate immune cells, leading to the development of a marked inflammatory response. AVP, arginine vasopressin; CO, carbon monoxide; HMGB1, high-mobility group box 1; HSPs, heat shock proteins; NO, nitric oxide; RAAS, renin–angiotensin–aldosterone system; SNS, sympathetic nervous system; TNF, tumour necrosis factor (68).

Pre-existing cardiac dysfunction and HRS

There is increasing evidence that cardiac dysfunction in the setting of CCM is associated with episodes of HRS (68). Koshy et al. attempted to stress cirrhotic hearts to determine whether cardiac dysfunction could predict the development of HRS by measuring CO at rest and during low dose

dobutamine infusion (70). Patients with HRS at the time of echocardiogram had an impaired chronotropic response with reduced change in heart rate (89.9% vs 110.8%, p = 0.002) and significantly lower survival probability. As part of this study, low cardiac reserve was also demonstrated to be a predictor for development of HRS (adjusted hazard ratio [aHR] 3.92, 95% CI 2.18-7.02, p <0.001) (70). A number of other studies have failed to demonstrate this association between cardiac dysfunction (in particular systolic dysfunction) and development of HRS, however, these studies only took into consideration assessments with resting echocardiograms (71, 72). Thus, dobutamine stress echocardiograms stand to inform about more than risk of atherosclerotic events alone. Detection of impaired cardiac reserve can assist in predicting adverse outcomes in advanced cirrhosis, including identifying patients at significant risk of HRS (70).

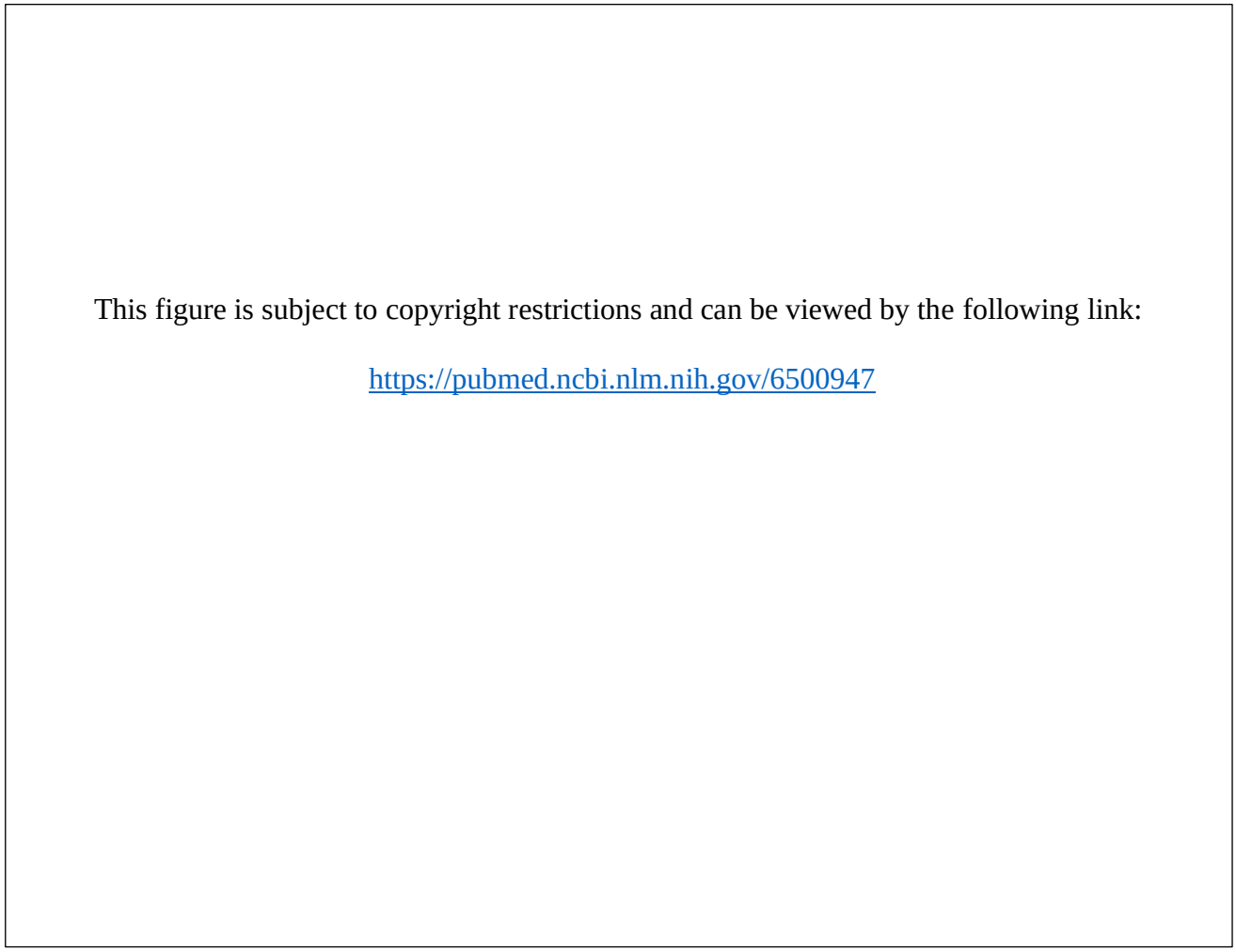

Figure 1.5: The diagnosis of HRS, reproduced from reference (68)

1.4.5.2 Diagnosis of HRS

HRS/AKI, previously referred to as "type 1" HRS, is the first subtype of HRS. The change in nomenclature was initiated by the Kidney Disease Improving Global Outcomes (KDIGO) as part of the consensus change to define AKI as more than an increase in serum creatinine (SCr) >1.5mg/dL (132umol/L) (Figure 1.5). Adapted from a comprehensive review by Gines et al., the current diagnostic criteria is as follows (68):

- Stage 1A: an increase in SCr ≥26.5 µmol/L up to 133 µmol/L
- Stage 1B: an increase in SCr ≥26.5 µmol/L to a value ≥133 µmol/L

- Stage 2: an increase in SCr greater than twofold to threefold from baseline
- Stage 3: an increase of SCr:
    - greater than threefold from baseline
    - ≥353.6 μmol/L with an acute increase ≥26.5 μmol/L
    - initiation of renal replacement therapy

HRS/AKI is recognised as a risk factor for adverse mortality in cirrhosis, in addition to adverse post-transplant mortality (67). The staging system provided by KDIGO assists in predicting the mortality risk associated with HRS/AKI..

The second subtype of HRS is related to those patients with less severe, or less acute, changes in estimated glomerular filtration (eGFR). Therefore, chronic kidney disease (CKD)-HRS is classified simply as eGFR <60mL/min/1.73m^2 for >3 months in the absence of other potential causes of kidney disease (73). Similar to the classification of HRS/AKI, diagnosing CKD/HRS relies on having a clear trend in the baseline creatinine levels to demonstrate progressive drop in eGFR. Identifying the difference between AKI/HRS and CKD/HRS is important as vasoconstrictors are less likely to be effective in the management of CKD-HRS.

1.4.5.3 Management of HRS

Guidelines recommend that other causes of AKI should be investigated in the workup for HRS (68). This includes pre-renal injury due to hypoperfusion, drug toxicity, and glomerulonephritis. Exclusion of structural kidney injury also continues to be part of the diagnostic criteria for HRS/AKI, however there are no biopsy-controlled studies of the merits and risks of biopsies in these patients (67). Despite how rarely it is done, renal biopsies in the setting of HRS/AKI can be useful in predicting renal function recovery and identifying glomerulonephritis that may persist post-transplantation (74). In

addition, patients with clinical manifestations of acute tubular necrosis (ATN) remain a diagnostic challenge, particularly given the differences in disease management. Traditionally, a fraction of excreted sodium was used to attempt differentiation between ATN and HRS, however, this methodology is weakened by solute deficiency and diuretic use, with most recent reviews removing it from the diagnostic algorithm (68). A recent review published in the New England Journal of Medicine emphasized the importance of volume expansion in all causes of AKI in cirrhosis (75). They recommend that diagnosis of HRS/AKI only occur after a 48 hour trial of volume expansion, discontinuation of nephrotoxins, and adequate treatment of sepsis (75). Acute tubular necrosis is a crucial differential to exclude, as the treatment is haemodialysis, and diuresis as needed, whereas the treatment of HRS/AKI requires vasoconstrictor therapy in addition to albumin (75).

After a fluid challenge and investigation for other causes of renal dysfunction, vasoconstrictors are the cornerstone in the management of HRS. They are usually combined with intravenous albumin to expand plasma volume. The recommended dosage is 20% intravenous albumin at 1g/kg/day for 2 days. Beyond its volume expansion capacity, albumin has been found to be an immunomodulator and antioxidant due to its ability to bind inflammatory mediators and reduce endothelial activation (73). The two standard of care vasoconstrictor therapies currently utilised include terlipressin and octreotide. Terlipressin is a synthetic vasopressin analogue that acts strongly on the splanchnic circulation (75). It is considered superior to octreotide, however, this may worsen ischaemia in patients with a history of CAD or peripheral vascular disease and is contraindicated in these subgroups of patients (73). Typical duration of treatment is one week to 10 days, after which either sustained improvement should be seen or transition to supportive care (75). In suitable candidates, liver transplantation needs to be explored where possible in HRS, as vasoconstrictor therapies are considered bridges to transplant rather than stand-alone treatments.

Despite all of the above therapies, full recovery of renal function is not universal, and this is primarily predicted by the duration of kidney injury. Furthermore, renal dysfunction and HRS have been found to be strong predictors of adverse cardiovascular events, and the impact of HRS on both short- and long-term post-transplant outcomes warrants further investigation (76, 77).

1.5 Diagnosis of CCM

The diagnostic criteria of cirrhotic cardiomyopathy in use until recently was that proposed in The 2005 World Congress of Gastroenterology as follows (54):

1. SD: blunted increase in CO with exercise, volume challenge or pharmacological stimuli; with resting LVEF <55%.
2. DD: prolonged deceleration time (DT, >200ms), prolonged isovolumetric relaxation time (>80ms), and E/A ratio <1
3. Supportive criteria: electrophysiologic abnormalities including abnormal chronotropic response; electromechanical dyssynchrony, prolonged QTc interval, enlarged left atrium, increased myocardial mass, increased BNP levels and increased troponin levels.

In the last 17 years, there have been significant advancements in the understanding and echocardiographic evaluation of cardiac dysfunction that are not reflected in these criteria. Advances in echocardiographic diagnostic techniques have led to a paradigm shift in the approach to the diagnosis of CCM. Moreover, with increasing awareness of the clinical significance, CCM has become implicated in the development of HRS, decompensation of end-stage liver disease, and morbidity and mortality following transplantation (5). The CCM consortium was formed consisting of hepatologists, cardiologists and anaesthetists. The formation of the CCM Consortium led to a

reconceptualization in the approach to diagnosing CCM. These changes are summarised in Figures 1.6 and 1.7. Recent reviews have encouraged the use of the new diagnostic criteria for CCM for both clinical and research purposes (16). The different diagnostic echocardiographic parameters for CCM, and the rationale for changing the diagnostic criteria, will be discussed below. These changes are also summarised in Figure 1.7.

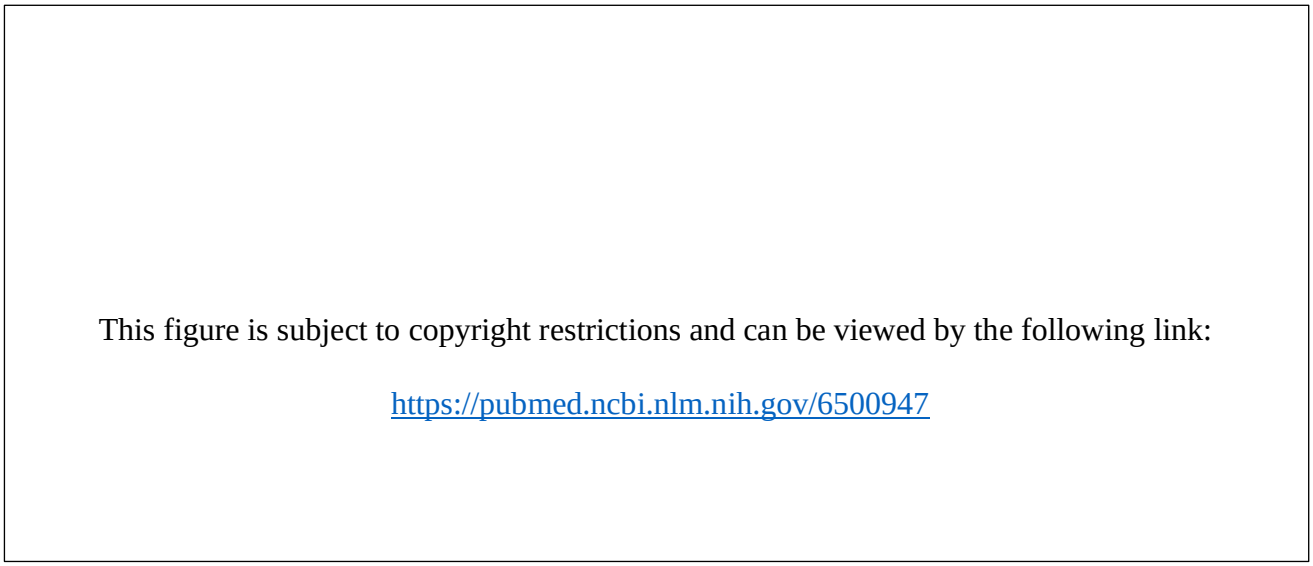

Figure 1.6: Proposed diagnostic criteria for CCM from the Cirrhotic Cardiomyopathy Consortium, reproduced from reference (5). CMRI, cardiac magnetic resonance imaging; GLS, global longitudinal strain; LAVI, left atrial volume index; LV, left ventricle; TR, tricuspid regurgitation.

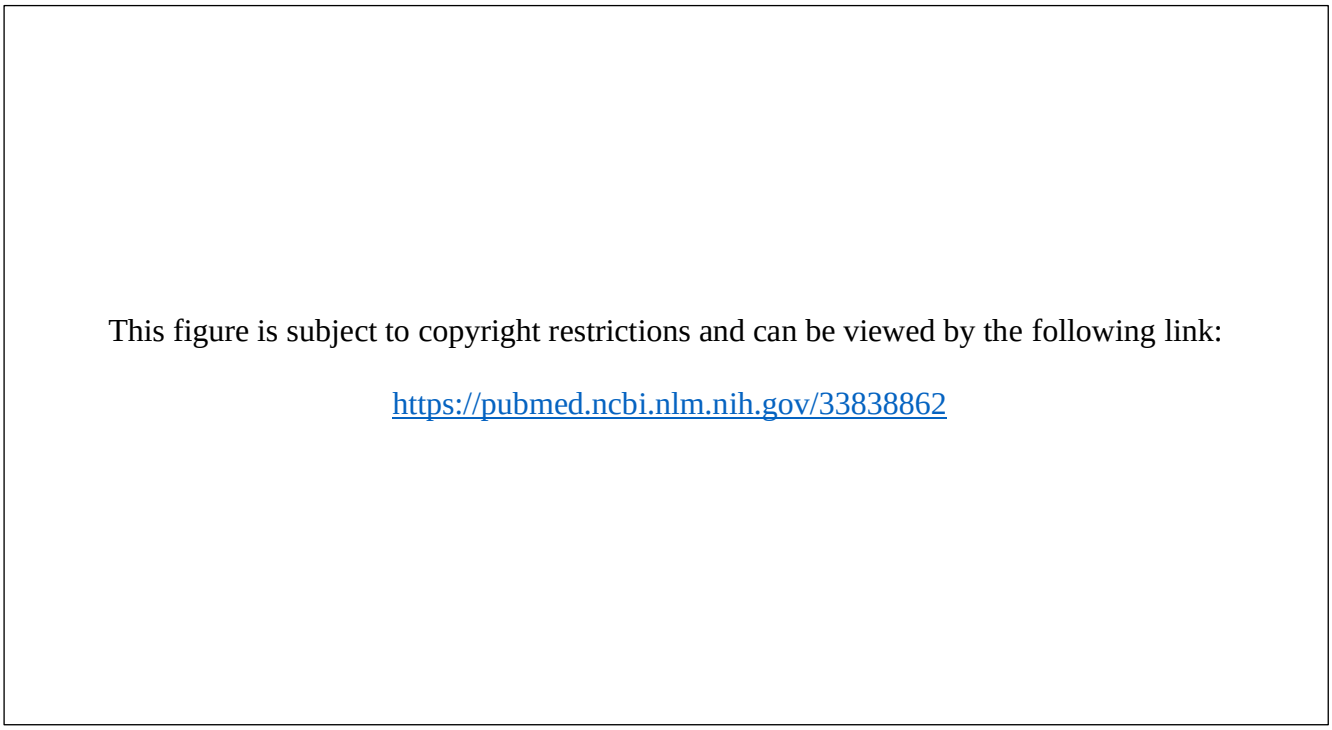

Figure 1.7: The revised criteria for CCM in comparison to the original criteria, reproduced from reference (78). GLS, global longitudinal strain; LAVI, left atrial volume index; LV, left ventricle; TR, tricuspid regurgitation.

However, the above diagnostic criteria lack correlation with clinical symptoms and signs of cardiac disease. Izzy et al. stress that identification of symptomatic heart failure is complicated in end-stage liver disease (ESLD) given the similarity in symptoms of heart failure to decompensated cirrhosis such as pleural effusions, peripheral oedema, and renal dysfunction (5). Singh et al. retrospectively compared the original CCM criteria to the one proposed by the CCM consortium (79). Whilst they found similar prevalence of CCM between both criteria (19.3% compared to 20.2%), the CCM consortium criteria allowed the recognition of advanced DD, which correlated with increased pre-transplant mortality and renal dysfunction (79). Overall, other studies highlight that the reported

prevalence of CCM using the newly proposed diagnostic criteria range from 27.5–34.7% (43, 80). This is slightly lower than previously estimated prevalence using the original WGO criteria (16) Evaluation for CCM is crucial, particularly for patients being considered for major surgery including LT or TIPSS, as it can be clinically silent, until the late stages of cardiac dysfunction.

1.5.1 Diagnosis of systolic dysfunction

Assessment of left ventricular systolic function has traditionally focused on the LVEF. The 2005 CCM criteria define SD by the presence of LVEF <55%, rest and/or a blunted contractile response on myocardial stress testing (e.g. failure of LVEF to increase on stress testing by >5%). The original criteria will be compared to the new diagnostic criteria below.

1.5.1.1 EF as a measure of SD

The vasodilatory state of ESLD results in decreased afterload and consequently, normal or even increased LVEF, where the typical cut-off is LVEF >70% (79). LVEF as a predictor of adverse morbidity and mortality in advanced cirrhosis was recently explored in a nationwide prospective study (81). An increase in LVEF was observed in MELD scores >20, and this is likely related to hyperdynamic circulation (81). In those patients with MELD >20, LVEF ≤60% was associated with worse 90-day ($p = 0.03$) and 5-year survival ($p = 0.003$) , thus questioning the LVEF cut-off of 55% to diagnose SD (81).

Over time, the diagnosis of cardiac failure has evolved to being classified as either heart failure with preserved or reduced EF. A normal EF is considered >50%, and an abnormal EF is <40%, with EF of 40-50% considered a “grey zone” with regard to management (5). With regard to the revised diagnostic criteria of CCM, the new definition of SD is <50% reflects the updated contemporary heart

failure nomenclature (5). Aghaulor and VanWagner also emphasized in a recent review that there is limited evidence for these EF cut-offs in advanced cirrhosis outside clinical experience (82). In addition to EF, the new CCM criteria includes tissue strain imaging for the diagnosis of SD, which will be discussed below.

1.5.1.2 Global longitudinal strain

Myocardial strain was first introduced in the 1990s, and the most commonly measured strain angle is global longitudinal strain (GLS). Strain is a measure of deformation of the myocardium. When there is early systolic dysfunction, strain imaging is capable of identifying impaired deformation, or in other words, impaired contractility of the left ventricle during systole (83). Radial and circumferential strain can also be measured but are difficult to accurately reproduce (84). Bright speckles are produced as a result of the scatter of the echocardiographic ultrasound beam, which are then used to track their displacement in myocardium during myocardial contraction (85). Speckle-tracking echocardiography is the most widely used modality to measure strain. Furthermore, systolic strain is also load dependent, and therefore blood pressure should be measured both at rest and after exertion for interpretation of strain measurements (84). Longitudinal strain is the most sensitive and earliest abnormality to occur in SD (84). Of note, GLS is measured as a negative number to reflect the percentage shortening of the myocardium with each systolic contraction. Other challenges associated with routine use of GLS include lack of standardisation of image processing and inter-radiographer variability in results.

The American Society of Echocardiography (ASE) classifies GLS by the following:

- GLS < -22% as abnormal, and a sign of hyperdynamic circulation
- GLS from -18% to -22% as normal
- GLS from -16% to -18% as borderline

- GLS > -16% as abnormal, and a sign of systolic dysfunction.

The CCM Consortium recommend that a GLS result that is less than -18% should be considered a sign of SD in the presence of LVEF >50% (5). In the setting of preserved LVEF, a high GLS score (more than -22%) is a sign of hyperdynamic circulation in advanced cirrhosis (83). Abnormal GLS can also occur independent of the presence of DD and is less influenced by changes in afterload and preload (83). The CCM Consortium also endorses the use of GLS as a diagnostic test for CCM (5).

A recent single-centre retrospective study reported a low prevalence of abnormal GLS in their cirrhotic population of 2% (80). This may be due to retrospective analysis of their TTE images. Another retrospective study of 117 LT candidates found that low GLS (above -18% for males and -17% for females) had a 13% prevalence and was an independent predictor of mortality in the setting of decompensated cirrhosis (p=0.002) (83). Interestingly a high GLS cut-off value (less than -26% for females and -24% for males) was also found to correlate with worse mortality, presumably as a marker of hyperdynamic circulation in advanced cirrhosis (Figure 1.8) (83).

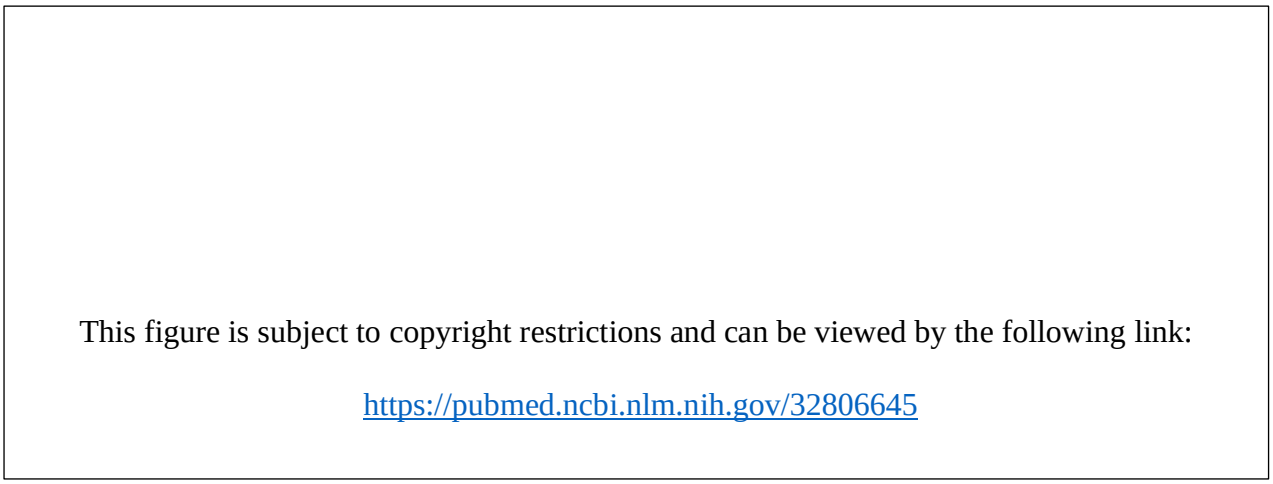

Figure 1.8: Kaplan-Meier survival curves showing survival probability based on GLS categories. values below −26 for females and −24 for males were defined as high, and values above −18 and −17 were defined as low. Reproduced from reference (83)

GLS is semiautomated and relies on high-quality technology in order to gain good quality images. Surprisingly, in a recent retrospective study comparing the original CCM diagnostic criteria to the new one, prevalence rates of GLS <-18% was above 90% when echocardiogram images were retrospectively analysed (79). Singh et al. argued that low GLS did not appear to predict adverse mortality in their cohort, however, this prevalence of subclinical SD is in stark contrast to other studies where low GLS had a prevalence of 10–20% (80, 83). The image quality and limited interpretation of old images could be an explanation for the wide variability in GLS in this study. Robust multicentre prospective studies that examine inter-observer variability are necessary to define the validity of GLS cut-off in CCM.

1.5.1.3 Myocardial response to stress

The subclinical LV dysfunction seen in cirrhosis has also been demonstrated to coexist with similar dysfunctions of the right ventricle, independent of the presence of pulmonary hypertension or hepatopulmonary syndrome (86). In a recent prospective study of cirrhosis and cardiac dysfunction on TTE, GLS and other multi-directional strain imaging was utilised in both the left and right ventricle. In this cohort, myocardial dysfunction was undetectable by conventional echocardiographic parameters (86). A healthy heart is expected to augment with exercise to induce at least 5% augmentation in EF (87). Impaired cardiac augmentation in cirrhotic patients with DSE has been demonstrated by an Australian study (70). However, assessment of impaired contractile response to stress testing is often limited in patients with ESLD. First, pharmacologic beta-blockade for variceal prophylaxis is commonly prescribed in the cirrhotic population, impeding the ability to achieve peak heart rate during testing. Secondly, intercurrent illness and tense ascites related to advanced decompensated liver disease further prevent patients from achieving peak exertion (7, 88, 89). The blunted adrenergic response manifests as limitations in myocardial contractility, otherwise known an

inotropic incompetence. This typically manifests as a higher baseline heart rate, low LVEF and reduced cardiac reserve (70). This is an early sign of CCM and it typically correlates with the development of ascites (16). It has not been included as part of the new diagnostic criteria for CCM. The CCM Consortium highlighted that documenting CCM through systolic and diastolic parameters, and advanced cardiac imaging and stress imaging could be much more informative. Stress echocardiography has been investigated in the diagnosis and prediction of clinical complications of CCM. Whilst DSE lacks sensitivity in detecting latent CAD or predicting adverse post-transplant coronary outcomes (89, 90), the blunted adrenergic response to stimuli corresponds to reduced myocardial reserve, demonstrated to be a predictor of HRS, a significant cause of mortality in advanced cirrhosis (70).

1.5.2 Diagnosis of diastolic dysfunction

The most well-established TTE finding of CCM is DD (16). DD has been associated with adverse clinical outcomes in decompensated cirrhosis in the peri-operative setting, as well as post LT and TIPSS procedures (91-93). The key TTE parameters used in diagnosing DD will be discussed below.

1.5.2.1 E:A ratio

The E:A ratio is conventionally used for reporting DD, as mentioned in the original CCM diagnostic criteria. E:A demonstrates the diastolic LV filling pressures as determined at the mitral inflow. E represents the velocity of early diastolic filling of the LV (which is a passive process) (94). In the earliest phases of diastolic disease (Grade 1) there is an initial reduction in E, however, as the filling pressure increases with progressive impairment of myocardial relaxation, E progressively increases (Figure 1.9).

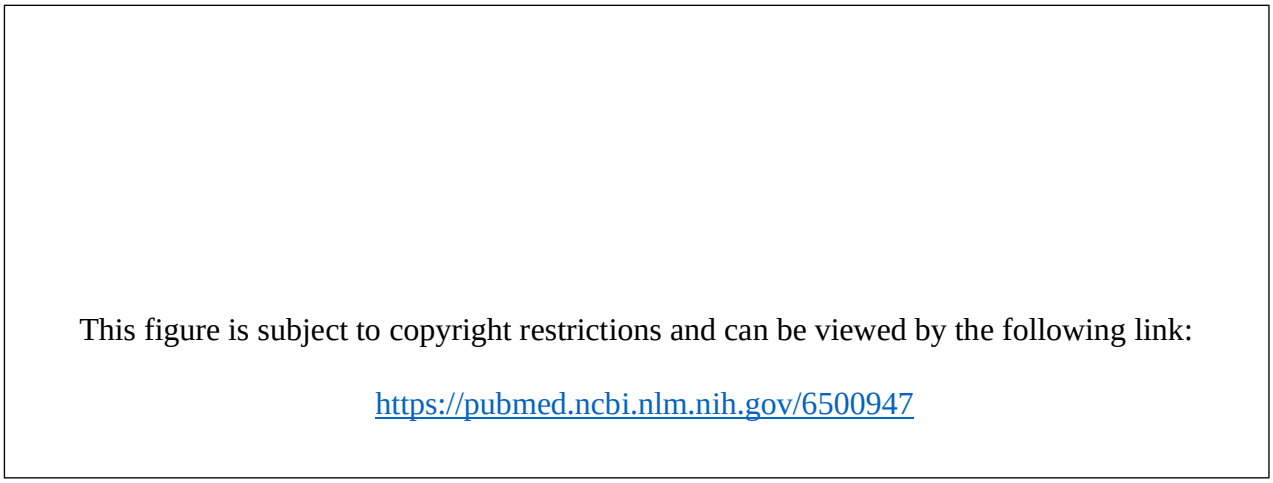

Figure 1.9: Changes in pressure, velocity and volume during different grades of diastolic dysfunction, reproduced from reference (5). Left ventricular myocardial inflow and relaxation is measured by e', and this is reduced in all forms of myocardial disease. E represents mitral inflow early diastolic velocity. During the early stages of diastolic dysfunction E is reduced, followed by a progressive increase with the progressive increase in filling pressures (5).

The A wave represents the final contraction of the atria into the ventricles. Whilst the A can initially compensate for impaired myocardial relaxation, this is not sustained, and A remains low as DD progresses. The E:A ratio lacks both sensitivity and specificity. In heart failure with preserved ejection fraction, including CCM, an abnormal E:A ratio is <1. The 2016 ASE highlight the fact that age-related change can cause a slowing of myocardial relaxation, which can account for a reduction in mitral E:A ratio (94). Given decompensated cirrhosis is also considered a state of "volume overload", reliance on E:A ratio may overestimate the degree of DD present without accounting for true failure of myocardial relaxation in the cirrhotic heart (79). Another issue with E:A ratio is the lack of applicability in the setting of atrial fibrillation/flutter. Additional variables can be added to improve the diagnostic accuracy of E:A ratio, rendering it a supplementary parameter rather than the primary modality for diagnosing CCM.

1.5.2.2 Other measures of DD

The original diagnostic criteria for CCM include prolonged deceleration time (>200ms) and prolonged isovolumetric relaxation time (>80ms) as indicators of DD. These are not routinely reported in standard TTE and as such their utility is limited. The 2016 ASE recommend that while these modalities can be combined with other mitral inflow parameters, they are affected by heart rate and arterial pressure, they are thus no longer included as recommended parameters to diagnose cardiac dysfunction. Therefore, they will not be discussed beyond this point and indeed their use in other retrospective studies of cardiac dysfunction in cirrhosis and LT candidates is limited to older, small case series (91).

1.5.2.3 DD using new criteria

The new diagnostic criteria for DD in CCM are based on Tissue Doppler imaging that measure intramyocardial velocities at mitral septal or lateral annulus insertion independent of flow (Figure 1.10). (95).

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Figure 1.10: Colour Tissue Doppler Imaging from the apical four chamber view sampling from the septal mitral annulus, reproduced from reference (95).

Measurement of e'

Tissue Doppler imaging is used at the mitral annulus to evaluate the lengthening and relaxation of the ventricle during diastole. The e' velocity corresponds with early rapid filling at the mitral annulus (94). Figure 1.9 clearly demonstrates the progressive drop in e' as diastolic dysfunction worsens, as such indicating increased left atrial pressure, and thereby the impaired relaxation of the heart that occurs in diastolic heart failure. Septal e' <7cm/second or lateral e' <10cm/second are both measures of diastolic relaxation and are measurements that can be made independent of preload status. While e' can be measured from either the septal or lateral annulus, the current recommendation is that e' is the average of both septal and lateral measurements (95). In the fluid overloaded state of decompensated cirrhosis, it remains a specific and accurate marker of myocardial relaxation (94).

E:e' ratio

E:e' ratio is abnormal when >14 and is a marker for advanced DD, provided there is no severe mitral annular calcification. This is measured using E, as mentioned above, as the early mitral inflow

velocity, whereas e' is the velocity at the mitral annulus (94). In the presence of DD, there is a slowing of the velocity at the mitral annulus (reduced e'), therefore the E:e' ratio becomes elevated in diastolic dysfunction. To measure E:e', either septal or lateral annulus images are taken. Generally, the septal annulus cannot move as freely as it is tethered to the right ventricle (96). Studies suggest measurement at the lateral annulus are more accurate in correlating with filling pressures (96). There is reduced accuracy when patients have regional wall motion abnormality in the setting of myocardial infarction, and in this situation it is advised to take an average of septal and lateral velocities to give the average E:e' (96). Other situations where E:e' is inaccurate include mitral valvular pathologies, or mitral valve replacement.

Left atrial volume

Left atrial volume index (LAVI) >34mL/m^2 is an indicator of severity and duration of DD, in addition to being a substrate and predictor of future atrial dysrhythmias. Isolated elevation of LAVI can occur in the setting of massive fluid overload, and as such additional parameters of DD are necessary (94). However, LAVI has previously been correlated with adverse cardiac outcomes post-transplant (92), and as such it is likely to continue to be a strong predictor of CVD in patients with ESLD.

Tricuspid regurgitation velocity

Tricuspid regurgitation velocity >2.8m/second is a marker of overload in the right heart. Elevations can be seen both in primary pulmonary vascular diseases and pulmonary venous congestion in the setting of fluid overload. Therefore, the CCM Consortium and 2016 ASE recommend it not be used in isolation for diagnosing advanced DD.

These four parameters are combined in an algorithm that guides the grading of DD (Figure 1.11). The benefits of such an algorithm include its simplicity and specificity given the number of parameters that are utilised. The definition and implication of indeterminate DD remains an area of ongoing exploration. In the absence of additional data, the 2016 ASE guidelines suggest the study to be inconclusive in this situation and therefore DD cannot be diagnosed (94). Furthermore, Singh et al. has recently demonstrated the specificity of diagnosis of advanced DD according to the new Consortium criteria, where they found that diagnosing advanced DD was more accurately associated with pre-transplant morbidity and mortality (79). Thirdly, impaired cardiac functional reserve has expanded beyond EF to include other parameters such as impaired diastolic reserve, an area that requires further investigation (5).

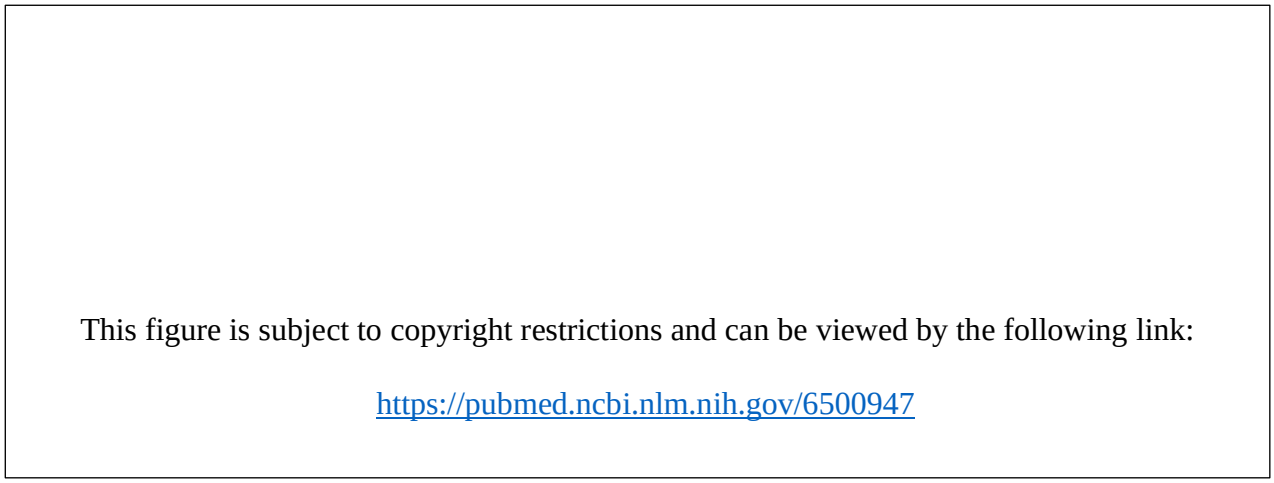

Figure 1.11: A simplified, revised algorithm for advanced diastolic dysfunction in patients with ESLD, reproduced from reference (5)

1.5.2.4 Novel emerging TTE parameters in CCM

Other echocardiographic modalities under exploration in the cirrhotic cohort include global myocardial work index, left and right atrial strain, and contrast echocardiography (97). A prospective

study of CCM in LT candidates that is currently being conducted in South Australia investigates investigational parameters of contractile reserve using global myocardial work index, to capture the changes that occur in the cirrhotic heart and correlate this with meaningful clinical outcomes such as development of AKI/HRS and mortality (98).

1.5.3 Biomarkers in CCM

1.5.3.1 Brain natriuretic peptide (BNP)

The precursor to BNP is known as pro-BNP. Pro-BNP is secreted by the left atrium in response to stretch, and cleaved into two fragments, BNP and NT pro-BNP (99). NT pro-BNP is measured preferentially to BNP as NT pro-BNP has a longer half-life of 120 min, making it a more reliable measure of myocardial dysfunction and fluid overload (99). NT pro-BNP has been studied in the randomised controlled trial setting and a good correlation of NT pro-BNP level to the progression and severity of cirrhosis has been shown (100). Pimenta et al. observed patients with decompensated cirrhosis and confirmed that NT pro-BNP levels in cirrhosis reflect cardiac dysfunction and the haemodynamic changes that occur in advanced liver disease (100). The reported median NT pro-BNP level was 103pg/mL among 83 patients with a median Child-Pugh score of 10 (100). In comparison, patients with decompensated cardiac failure often have much higher BNP levels, up to the thousands (101). A prospective observational study of serum BNP levels in cirrhotic patients with incidentally detected DD found that BNP was nearly double (mean 447pg/mL) in patients with DD compared to those without (mean 277pg/mL) (102). At this stage, there remains a lack of sufficient data to guide appropriate cut-offs to detect cardiac dysfunction in the cirrhotic cohort.

1.5.3.2 Troponin

Troponin is a biomarker of myocardial damage, which can be used in conjunction with appropriate history of chest pain and electrocardiographic changes to diagnose myocardial infarction (MI). However, troponin lacks specificity and often fails to identify the type of myocardial event occurring; whether it is a type 1 MI in the setting of a plaque event compared to a type 2 demand-related cardiac ischaemia in the setting of intercurrent illness. Furthermore, given its renal clearance, troponin can also be falsely elevated in the setting of renal dysfunction. Despite these limitations, it was found to be a reliable marker of peri-operative and post-transplant adverse outcomes in one retrospective study (103). Watt et al. found pre-transplant troponin elevation and pre-transplant CAD were both strong predictors of mortality and graft loss in the LT population (103).

1.5.3.3. Electrocardiographic changes

The QT interval is the distance in time between commencement of atrial contraction (Q), to the end of ventricular repolarisation (T), as such depicting an entire cardiac cycle (104). The corrected QT, otherwise known as the QTc, corrects the QT interval for the heart rate, and the QTc is relied upon for diagnosis of prolonged QT, a known risk factor for polymorphic ventricular tachycardiac and sudden cardiac arrest. Defined cut-offs include borderline QTc (>440milliseconds), QTc >450milliseconds in males and QTc >460milliseconds in females (105). QTc prolongation has also been demonstrated to correlate closely with the degree of liver decompensation (35). Bernardi summarised the ECG changes in CCM as chronotropic incompetence (106), which is exemplified by the prevalence of QTc prolongation, up to 60% more, compared to non-cirrhotic individuals.

With regard to the pathophysiology of QT prolongation in cirrhosis, the exact mechanism remains unclear. There is delayed repolarisation of cardiac myocytes in cirrhotic patients, which is measured

using the QT interval (106). Potential contributing factors include sympathetic nervous system upregulation, disequilibrium in electrolyte levels, and systemic inflammation are all potential contributors (45). Additionally, there is depletion of L-type calcium channels and potassium channels in the myocardium of cirrhotic patients. Calcium dysregulation can trigger cardiac myocyte apoptosis and subsequent QT prolongation (60). The increased prevalence of QT prolongation observed in cirrhosis is thought not to correlate with increased risk of life-threatening ventricular arrhythmias (106). A review of relevant pharmacotherapy that may be contributing to QT prolongation and correction of underlying electrolyte imbalance becomes the preferred management method when QT prolongation is detected in cirrhosis.

Overall, the clinical relevance of the QT prolongation remains uncertain (106), with resolution seen in most patients after LT. This has previously been explored in a retrospective audit by Kim et al., where very prolonged QTc >500ms was associated with a significant increase in 30-day major adverse cardiovascular events post-transplant. The presence of prolonged QTc also correlated with electrolyte imbalance and advanced liver disease in the lead-up to transplantation (107). Koshy et al. also presented similar findings, where QT prolongation >480ms was strongly associated with post-transplant cardiac arrest or ventricular arrhythmia (108). In the original diagnostic criteria of CCM, QT prolongation was considered one of the supportive criteria, however, Koshy et al. argued that among their Australian LT candidates, there was no correlation seen between QT prolongation and structural or functional cardiac changes of CCM (108). Many studies that investigated QTc as a surrogate marker of CCM failed to find an association with adverse cardiovascular outcomes both pre- and post-transplant (109). Therefore, while QT prolongation has been correlated with adverse outcomes post-transplant, its pathophysiology may well occur independent of CCM. The utility of

close surveillance for those with very prolonged QT or the use of beta blockers to prevent ventricular arrhythmias (if safe to do so) requires further investigation (110).

1.5.3.4 Cardiac MRI

Cardiac MRI appears to be a promising investigative tool in all forms of cardiomyopathy, with the added benefit of not exposing patients to radiation (111). There are several advantages to the evaluation of the cirrhotic heart using cardiac MRI as demonstrated in several studies in both compensated and decompensated cirrhosis. Cardiac MRI has the ability to measure LVEF with high accuracy, compared to echocardiography, where images are operator-dependant (97). Furthermore, a unique parameter to cardiac MRI is the quantification of the extracellular volume (ECV) fraction. ECV has been found to be a reliable predictor of diffuse (and reversible) interstitial fibrosis within the myocardium and is a precursor to the permanent changes that occur when late gadolinium enhancement (LGE) is seen. LGE is a diagnostic feature of significant (and irreversible) subendocardial fibrosis (112). Isaak et al. also found that myocardial changes in cirrhosis progress with greater severity of liver disease (112). In an observational study of LT candidates, cardiac MRI demonstrated that increased ECV in cirrhotic patients was significantly correlated with disease severity and transplant-free survival (113). In a longitudinal study, LT candidates were followed through transplantation with serial cardiac MRIs, demonstrating normalisation of ECV in addition to improvement in LVEF (17).

Cardiac MRI remains as a strong alternative for the investigation of resting ventricular volumes, ejection fraction, myocardial ischaemia, detection of reduced myocardial reserve, and characterisation of early or advanced myocardial fibrosis (97). GLS abnormalities have been shown to correlate with ECV changes in cirrhotic patients (17). GLS can therefore be considered a surrogate

marker for the structural changes of CCM (17). Despite the accuracy of cardiac MRI, it carries some limitations including patient tolerability, presence of metallic foreign objects that prohibit MRI use, and patient stability given the time taken to perform an MRI. Furthermore, not all MRI machines are capable of imaging the heart, and their cost render them restrictive for some transplant centres. Cardiac MRI continues to be a research tool rather than an investigation available for routine clinical practice. Further clinical trials and research are needed to address the role of cardiac MRI in the workup of LT candidates.

1.6 Impact of CCM on clinical outcomes

CCM is asymptomatic at rest due to the excess vasoactive mediators in advanced cirrhosis. During periods of stress such as LT surgery or TIPSS the fluctuations in fluid balance can precipitate overt cardiac dysfunction. Outside LT, the impact of CCM on clinical outcomes in advanced cirrhosis is less studied. A recent systematic review including over 1000 patients demonstrated that the prevalence and severity of DD increased with progressive worsening of decompensated cirrhosis (114). Earlier studies (prior to the revised CCM Consortium) investigated the separate components of the CCM diagnostic criteria in relation to clinical outcomes in cirrhosis. A prospective study found that DD (measured using E/e') correlated with a significant reduction in survival among patients with cirrhosis ($p = 0.01$) (115). Karagiannakis et al. also demonstrated that advanced cirrhosis (measured using Child-Pugh Score) correlated with a high prevalence of DD and worse survival, advocating for strict follow up of these patients (39).

SD is less commonly detected in CCM, particularly using the original diagnostic criteria which relies on LVEF, despite the central hypovolaemia in advanced cirrhosis (116). Abnormal GLS was

prospectively studied in one cohort to assess correlation with worse survival after TIPSS procedure (117). When TIPSS was performed in patients with GLS higher than -16.6%, these patients were found to have acute on chronic liver impairment and reduced survival compared to patients with normal GLS.

1.6.1 CCM as a predictor of post-transplant morbidity and mortality

The presence of DD is associated with peri-operative myocardial dysfunction among the general population undergoing non-cardiac surgery (118). Similarly, CCM is the most important risk factor for post-transplant adverse cardiac complications in the LT population, given its prevalence of up to 40% in some studies (119). Table 1.1 summarises the literature that has evaluated the association between cardiac dysfunction and adverse post-transplant morbidity and mortality. Izzy et al. found post-transplant CVD was significantly more frequent in patients with pre-transplant CCM as defined by the revised CCM consortium criteria (HR 2.57, 95% CI 1.19-5.54, p = 0.016), where CVD was defined as a composite of CAD, heart failure, arrhythmia or stroke (80). Following this publication, Singh et al. compared the utility of the original World Congress of Gastroenterology CCM diagnostic criteria (2005) to the revised CCM Consortium diagnostic criteria, finding that advanced DD per the Consortium criteria had a higher trend to predicting pre-transplant mortality (79). DD has been the most common parameter studied. Qureshi et al. and Mittal et al. further quantified the degree of DD detected and concluded that severe (grade 3) DD was associated with worse survival outcomes (40, 120). As can be expected, Sakr et al. found that LVEF <40% was a strong predictor of 1- year mortality post-transplant. However, this was the only group to use this LVEF cut-off, which can be argued is excessively low and lacks sensitivity in the setting of hyperdynamic circulation of cirrhosis (121).

Table 1.1: Summary of studies investigating the incidence and predictors of post-transplant morbidity and mortality in the context of CD.

Investigators	**Number patients**	**Definition of CD**	**Post-transplant morbidity**	**Post-transplant mortality**
Qureshi et al.(120)	945	E/A and E/e', graded 1-3	Pre-LT DD associated with post-transplant HF, based on grade of DD. Other predictors include HRS/AKI, BMI, hemodynamic	Post-transplant HF associated with increased mortality SD predicted mortality
Izzy et al. (80)	141	2019 CCM Consortium diagnostic criteria	CCM increased risk of post-transplant CVD	CCM did not increase all-cause mortality
Sonny et al. (122)	327	2016 ASE criteria for DD and QT	Pre-transplant DD strongest predictor of post-transplant heart failure (incidence rate 6%)	No association between DD and mortality. QT associated with mortality, graft failure and MACE
Kwon et al. (81)	2799	LVEF, arterial elastance, LVEDP, EDV	Not examined	EF <60% and MELD >20 associated with worse post LT mortality and graft failure
Dowsley et al. (92)	107	SD: LVEF DD: E:e', LAVI, E/A	24% had HF post LT LAVI and high E:e' predictors of SD and HT post-transplant	LAVI >40 associated with higher all-cause mortality
Sakr et al. (121)	176	HFrEF <40% E/e', E/A, DT, PAP	High peri-operative transfusion and pre-op HF predicted post-op HF	Post LT HFrEF 14% and strong predictor of 1 year mortality
Mittal (40)	970	E/A and E/:e'	DD predictor of ACR and graft failure	DD predictor of all-cause mortality
Raevens et al. (123)	173	SD: <55% DD: E/A and DT	No difference	No difference
Josefsson et al. (93)	234	SD: EF<50% DD: E/A <1	Heart failure occurred in 27%, but not associated with pre-LT DD	Post-transplant heart failure and dialysis predict mortality

Some single centre studies failed to show an association between DD and adverse post-transplant events (121, 123). Additionally, not all studies excluded patients with pre-existing CVD, further

increasing the heterogeneity of results. While Sonny et al. did not demonstrate an association between pre-transplant DD and post-transplant CVD or cardiac mortality (122), it was shown that in the presence of DD, post-transplant CVD worsened over time with an increase in left ventricular mass over a median of 41 months. DD was also a predictor of post-transplant systolic heart failure (122). However, many other studies have also highlighted the lack of association between pre-transplant DD and post-transplant cardiovascular outcomes (121, 123).

When examining specific echocardiographic parameters for predicting post-transplant cardiac failure, the strongest evidence lies in LAVI, where LAVI >40 mL/m2 was shown to be associated with post-transplant heart failure and post-transplant mortality (80, 92). Izzy et al. also found that a pre-transplant GLS cut-off value of <-20.6% (which is higher than the threshold used in the general population of -18%) was also an independent predictor of both post-transplant heart failure and CAD (HR 6.02, 95% CI 91.26-28.7, p 0.024 and HR 6.51 95% CI 1.30-32.7, p 0.02 respectively) (80). Furthermore, Mechelinck et al. demonstrated that both low GLS (related to SD) and high GLS (related to hyperdynamic circulation) were associated with worse survival overall (83). Overall, the hypothesis is that CCM patients, particularly those with severe or advanced disease, developed unfavourable outcomes post-transplant due to the inherent myocardial dysfunction accrued pre-transplant. Josefsson et al. and Qureshi et al. had similar findings in their retrospective single-centre studies (93, 120). The salient message from these studies is that accurate detection of myocardial dysfunction is necessary for cirrhotic LT candidates.

Pre-transplant cardiac dysfunction due to any cause appears to be a significant risk factor for acute and long-term post-transplant CVD. Additionally, myocardial dysfunction appears to be one of the earliest manifestations of oxidative stress and vascular inflammation, both of which are known

mechanisms for the development of CAD, thus explaining why CCM and other causes of cardiac dysfunction are correlated with post-transplant CAD (124). More data using the new CCM diagnostic criteria is needed to help risk stratify patients who are unsuitable, or high risk, for LT in larger, multicentre and prospective trials.

1.6.2 Reversibility of CCM post-transplant

There is progressive restoration of portal hypertension over 6 months after a successful LT. Generally, the first 3 months following transplantation is high risk with regard to immunosuppression dose, risk of infection and fluid balance. During the LT procedure the dramatic increase in preload could result in fluid overload and decompensated heart failure (125). Destabilisation in LVEF and diastolic function in the early post-operative period was frequently demonstrated in single centre studies (92). Qureshi et al. found that pre-transplant hypotension was an independent predictor of early post-transplant heart failure (120).

Torregrosa et al. studied LT recipients with pre-transplant cardiac dysfunction and successfully demonstrated that in the 6-12 months post-transplant, there is eventual improvement in left ventricular mass and exercise capacity (42). Prospective studies of cirrhosis and myocardial extracellular volume (ECV) using cardiac MRI also demonstrated improvement in hyperdynamic circulation and normalisation of ECV at 1-year post-transplant, suggesting that CCM changes in LT have the potential to improve after successful LT (17, 113). However, both these studies had small sample sizes and none of the patients had severe cardiac dysfunction pre-transplant. Chen at al. followed a small cohort of LT candidates to 1-year post-transplant, finding that the subclinical low-normal GLS pre-transplant of -18.5% +/- 2.6 improved significantly to -20.8% +/- 2.0 post-transplant (2). Paediatric studies of CCM have also demonstrated that in mild CCM, reversal of structural TTE

changes occurred in all cases (126). Conversely, Sonny et al. found that with longitudinal follow-up over a median of 4.2 years, SD appeared to persist post-transplant and the DD grade worsened over time (122), suggesting the persistence of myocardial dysfunction in a subset of patients with severe cardiac dysfunction. It is possible that there is a threshold of cardiac dysfunction beyond which irreversible and clinically significant myocardial damage occurs. Qureshi et al. demonstrated that grade 3 DD had significant association with adverse mortality (120), whereas patients with mild to moderate DD may reverse post-transplant.

Diastolic heart failure is defined according to the European Society of Cardiology task force, as follows: (1) symptoms or signs of heart failure; (2) normal or mildly reduced LVEF (LVEF > 50% and LV end-diastolic volume index < 97 mL/m2); (3) evidence of abnormal LV relaxation, filling, diastolic distensibility, and diastolic stiffness (127). Heart failure with reduced ejection fraction (HFrEF) is defined as clinical signs and symptoms of heart failure, in addition to LVEF ≤40% (127). Pre-transplant, decompensated cirrhosis can also present with all of the above signs, masking overt cardiac dysfunction. The predominance of post-transplant heart failure described in section 1.9.2 suggests that echocardiographic abnormalities identified pre-transplant may well be representative of cardiac failure and hence the presentation as overt heart failure post-transplant. Improving awareness of CCM pre-transplant is crucial to early, rapid diagnosis of heart failure as a potential comorbid issue in the peri-operative period. Further studies are needed with longer follow-up to assess CCM changes in both mild and severe manifestations of CCM.

1.7 Management of CCM

There is no specifically approved treatment for CCM. A high index of clinical suspicion is essential as CCM is usually clinically asymptomatic. Appropriate echocardiographic evaluation for CCM in

high risk patients such as those undergoing LT evaluation, TIPSS or refractory hypotension with beta blockers may lead to the diagnosis. In the setting of overt clinical failure, intravenous frusemide, supplemental oxygen and afterload reduction are all recommended. However, caution should be exercised due to the increased risk of renal dysfunction in the setting of low systemic arterial pressures (46).

1.7.1 Beta blockers

Beta blockers are primarily used in hepatology as primary and secondary prophylaxis of variceal bleeding. A commonly used non-selective beta-blocker such as propranolol reduces CO and splanchnic blood flow, while the unopposed effect of alpha-1 adrenergic receptors results in splanchnic vasoconstriction (128). Carvedilol is the preferred agent for primary prophylaxis of variceal bleeding due to specific anti-alpha one receptor activity that significantly reduces portal hypertension. Often in patients with profound decompensated cirrhosis and refractory ascites, beta blocker use has been associated with renal dysfunction and increased mortality risk (129). It is postulated that the low cardiac reserve that has been demonstrated in advanced cirrhosis may not tolerate further diminishment of CO with use of beta blockers (70). Beta blockers including carvedilol have been extensively studied in the prevention of cardiac remodelling in heart failure (130). However, evidence for benefits of beta blockers in CCM is limited. In a randomised controlled trial of metoprolol use for 6 months in CCM, there was no significant difference in clinical events, mortality, or changes in cardiac function (131). Other studies have shown that beta blockers reduced right ventricular strain or QT prolongation in the setting of CCM, but there is a lack of long-term clinical follow-up to suggest whether these changes improve morbidity and mortality in this population (16).

1.7.2 Other heart failure therapies

In the management of heart failure in the general population, the RAAS system is typically targeted using three agents; beta blockers, angiotensin converting enzyme (ACE) inhibitors and mineralocorticoid receptor blockers. These agents have the strongest evidence base in improving morbidity and mortality in heart failure with reduced ejection fraction. Spironolactone is commonly used in the management of ascites and peripheral oedema in decompensated cirrhosis. The use of spironolactone has been explored regarding its ability to reduce portal pressure, which was quantified by measuring hepatic venous pressure gradients (132). However, another study found that while spironolactone was successful in lowering hepatic venous pressure gradient, after 6 months of spironolactone use, it did not translate to structural improvements in cardiac function (133). Aldosterone antagonists have also been trialled previously for CCM (67). In a brief study of early cardiac dysfunction, aldosterone antagonism led to a decrease in left ventricular wall thickness and no worsening of cardiac dysfunction (67). However, this study was limited by a brief intervention period (6 months) and low case numbers (133). Adverse effects of spironolactone include electrolyte disturbance, problematic gynaecomastia, and AKI. The use of positive inotropic agents has fallen out of favour among all forms of cardiomyopathies, unless all other therapies have failed, due to their lack of mortality benefit. Therefore, the use of cardiac glycosides such as digoxin are contraindicated in cirrhosis, in particular due to its lack of efficacy (134).

1.7.3 Albumin

Endogenous albumin is synthesised by the liver and is the main contributor to maintaining the osmotic pressure in circulation (135). Albumin is one of the largest proteins in human circulation, it carries a negative charge, and generates a high oncotic pressure to maintain plasma volume (62). Albumin has the ability to bind to a wide range of ligands including heavy metals, fatty acids, bilirubin and drugs,

maximising bioavailability (62). In the setting of hypoalbuminaemia, it can be administered exogenously in either 40g/L or 200g/L concentrations. The benefits of albumin have been explored in decompensated cirrhosis with a recent open-label prospective trial randomising patients to either 20g twice per week albumin or standard of care. There was a significant reduction in accumulation of ascites ($p = 0.002$), infections ($p = 0.001$), and hepatic encephalopathy ($p = 0.016$). The incidence of HRS trended towards significance, but statistical significance was not reached ($p = 0.084$) (136). Albumin continues to be routinely used in the prevention of circulatory dysfunction related to large volume paracentesis and HRS. Studies are ongoing regarding the use of long-term albumin administration and whether there is a survival benefit in cirrhosis (62). Beyond these hard outcomes, albumin acts as both an antioxidant and a scavenger of free radicals and an immune modulator (137). Another study showed that albumin is internalised by white blood cells, which subsequently downregulates immune activation from pathogens while also consuming and accelerating degradation of the albumin molecule (135). The benefit of albumin is therefore likely to be beyond plasma volume expansion, relating also to its modulation of systemic inflammation in the setting of cirrhosis.

In the setting of CCM, there is a theoretical risk of volume overload with albumin administration. This has been explored in a prospective single-centre study, which found an incidence rate of 30% of volume overload in those having regular albumin infusions (138). The presence of DD was not a predictor of fluid overload, nor was there an improvement in clinical outcomes with regular albumin infusions (138). Thus, there is limited evidence to support the use of regular albumin infusions in the management of CCM.

1.7.4 Left ventricular assist devices

Increased recognition of CCM has allowed patients to access advanced heart failure therapies such a left ventricular assist device (LVAD). While these are typically considered as a bridge to heart transplant, promise of favourable cardiac transplant-free survival was recently demonstrated in a single-centre retrospective review by Dandel et al. (139). In patients with severe CCM, after weaning from the LVAD the 5-year freedom from heart failure recurrence reached 66%, even in those patients with incomplete cardiac recovery (139).

1.7.5 The role of LT in CCM

LT is the most effective treatment for patients with advanced liver disease who are deemed suitable candidates. Whilst LT is thought to improve most of the myocardial and structural abnormalities seen in CCM (13), CCM is also correlated with adverse cardiovascular outcomes in LT recipients (13). In one retrospective study, CCM was associated with post-transplant cardiovascular disease (hazard ratio of 2.51, 95% CI 1.13-5.57) without worsening post-transplant survival (80). However, this case series, similar to other earlier studies, was a retrospective. Chapter 2 will present the transplant outcomes of patients with cardiac dysfunction in the South Australian liver transplant cohort. Large prospective studies are required to gauge the risk of post-transplant CVD in CCM patients in addition to the reversibility of CCM. A thorough cardiovascular pre-transplant assessment is crucial to informing which patients deserve cardiac optimisation prior to LT.

1.8 Cardiac dysfunction in TIPSS

TIPSS is a non-surgical way to reduce and manage complications of portal hypertension. It serves as an alternative to and at times a bridge to successful LT (140). Using an endovascular stent, an artificial shunt is created between the portal vein and the hepatic vein. By reducing vascular resistance through

the liver, TIPSS acutely increases the preload to the heart, with an estimated increase of 3-5 mmHg in right atrial pressure. Pre-existing DD may prevent the accommodation of a sudden increase in preload and has the potential to exacerbate any underlying cardiac dysfunction. The current indications for TIPSS include patients requiring at least three large volume paracentesis per year, hepatic hydrothorax, and recurrent variceal bleeding. Potential complications include cardiac decompensation, pulmonary hypertension, hepatic encephalopathy and renal dysfunction. The North American Practice-Based Recommendations have emphasised the importance of a team-based approach for assessing TIPSS suitability, with the team to include a hepatologist and an interventional radiologist with competency in TIPSS, with additional input from cardiology, respiratory and nephrology for complex cases (141). These guidelines cite CCM as a significant factor for post-TIPSS heart failure. One study found the leading cause of death following TIPSS to be cardiac failure, and the prevalence of post-TIPSS cardiac dysfunction to be up to 20% (142). A left ventricular ejection fraction (LVEF) of <50% or grade 3 DD are cited as contraindications to TIPSS due to the risk of post-transplant cardiac decompensation. A prospective study of cardiac dysfunction post-TIPSS found that 20% of patients developed cardiac dysfunction at 1 year, with any pre-TIPSS DD and elevated BNP levels prior to TIPS found to be key predictors (142). Given the mortality and morbidity risk in patients with cardiac dysfunction prior to TIPSS, current guidelines emphasise the importance of considering the risks and benefits of TIPSS, in addition to having a staged approach to TIPSS creation initially at 8mm followed by clinical assessment for control of symptoms (141). The North American practise-based recommendations for TIPSS guidelines also recommend a routine echocardiogram at 3 months post-TIPSS to detect any deterioration in cardiac function.

While still experimental, the possibility of utilising TIPSS in the management of hepatorenal syndrome (HRS) remains on the horizon. A meta-analysis of 9 studies showed that TIPSS

significantly improved renal dysfunction with an 83% overall response rate (81). However, the validity of the findings was limited by the heterogeneity and small sample sizes of the review studies. HRS can often coexist with a degree of myocardial dysfunction, while the manifestations of refractory ascites can mask the presence of clinical cardiac dysfunction (141). Therefore, while TIPSS appears to be a promising treatment for selected patients with vasoconstrictor-responsive HRS, it can diminish cardiac reserve in these patients resulting in further cardiac decompensation. Jansen et al. found that GLS was a predictor of overall mortality and acute on chronic liver failure among TIPSS recipients (hazard ratio 1.123, 95% CI 1.101-1.250) (117). Low GLS had a higher area under the receiver operating characteristic curve than MELD score or chronic liver failure consortium acute decompensation (CLIF-C AD) score (117). This is the first study to demonstrate that GLS was the best predictor of adverse outcomes in TIPSS. Their findings suggest a GLS cut-off of -16.6% to predict ACLF and death in the setting of TIPSS (117).

1.9 Cardiac workup in liver transplantation

1.9.1 Introduction

Due to major advances in the technical aspects of LT surgery, quality of donor organ, peri-operative management, and immunosuppressive management the overall survival of LT recipients has improved significantly over time (143). However, CVD remains a challenge post-transplant with a cumulative incidence of up to 30% over 8 years post-transplant (144). The term “cardiovascular disease” has previously been used interchangeably with “coronary artery disease”. However, the true definition according to the American Heart Association (AHA) includes any condition that affects the heart, including CAD, heart failure, arrhythmias and valvular heart disease, in addition to extra-cardiac diseases including stroke, peripheral artery disease venous thromboembolism and pulmonary hypertension (89). This section will focus on the impact of those conditions that affect the heart

primarily, including CAD, heart failure, arrhythmias and valvular heart disease, in addition to a specific focus on porto-pulmonary hypertension (PPHTN), and hepatopulmonary syndrome (HPS).

The exact prevalence of CAD in LT candidates is difficult to quantify as previous studies limit coronary angiography (CA) to those with abnormal cardiac imaging or significant risk factors, resulting in sampling bias (9, 145). In a registry study of cirrhotic patients matched to non-cirrhotic patients with similar cardiovascular risk factors, the prevalence of CAD did not differ based on presence or severity of liver disease (7.2% versus 7.9%) (146). As the mean age of LT candidates increases, so does their comorbidity profile. A comprehensive pre-transplant cardiac evaluation for CVD is integral to improving LT outcomes. However, current liver transplant guidelines need to recognise the recent advances in the field of cardiac diagnosis and apply them to LT candidates (33, 147). A recent critical appraisal of the current literature identified some of the key issues and knowledge gaps in the management of CVD specifically in LT, including optimising the treatment of metabolic syndrome and using the patient's cardiovascular risk profile to gauge post-transplant follow-up (144). The objectives of this section will be to describe the burden of CVD in LT candidates and its impact on outcomes, the risk factors of CVD to consider during LT assessment and summarise contemporary evidence-based recommendations for cardiac workup of LT candidates.

1.9.2 Prevalence of CVD in LT candidates

Many observational studies have demonstrated the variation of CAD prevalence based on the aetiology of cirrhosis. Gologorsky et al. presented findings of over 17,000 LT recipients; those patients with MAFLD cirrhosis had the highest prevalence of CAD (7.4%) in comparison to biliary cirrhosis (1.7%) and alcohol (2.9%) (145).

Data from the Australian Institute of Health and Welfare demonstrate a reduction in cardiovascular-related mortality among the general population from 3,000/100,000 to just under 1,000/100,000 deaths using international classification of diseases (ICD) codes (148). This is largely due to improvements in both medical and procedural treatments for acute coronary syndromes, and increased recognition and treatment of cardiovascular risk factors.

1.9.3 Risk factors for CAD in LT candidates

The AHA and the American College of Cardiology Foundation (ACCF) have previously described risk factors of CAD in LT candidates as age >60 years, prior CAD, hypertension, DM, smoking, and left ventricular hypertrophy (149). This risk factor list is unlikely to be sufficient to accurately identify those LT candidates that harbour latent CAD. The prevalence of CAD in LT candidates was estimated at 2.7%-7.4% in population studies from 2004 to 2006, varying by the presence of cardiovascular risk factors (125). However, updated prevalence studies have shown that this is a significant underestimate of CAD prevalence in LT candidates. A recent systematic review and meta-analysis by Xiao et al. found that the pooled prevalence of pre-transplant CAD to be 15.9% among LT candidates, however, this study was hindered by heterogeneity in definitions and diagnosis of CAD in pre-transplant workup (150). Xiao et al. also explored risk factors and their prevalence in LT patients. They found that older age, male gender, type 2 DM, hypertension, hyperlipidaemia, smoking and MAFLD were all highly significant pre-transplant risk factors of CAD (150). Additional non-traditional cardiovascular risk factors included hepatitis B infection (OR 1.4, 95% CI 1.2-1.6, $p = 0.003$), and hepatocellular carcinoma (OR 1.6, 95% CI 1.2-2.0, $p = 0.02$), which were both found to be significantly associated with pre-transplant CAD (150). In 2015, Fussner et al. demonstrated that LT recipients with CAD have 2–3 times the mortality of age and gender matched patients in the general population (151). However, a few recent prospective studies have demonstrated equal

survival outcomes in LT candidates that have had appropriate revascularisation to those patients who do not have CAD (7, 9, 152). This discrepancy is worth noting, as over the time-course of these studies, the comorbidities of patients being considered for LT has remarkably changed. Furthermore, most of the included studies in the meta-analysis have a selection bias, as it reflects only those patients thought to be well enough for transplantation in the first place (150). The unmet need for better recognition of cardiovascular risk factors and non-invasive screening for CVD is crucial to providing equitable access to LT, and improve post-transplant outcomes.

The accumulation of cardiovascular risk factors as predictors of significant and severe CAD in LT candidates was intricately explored in a case series (149). Two or more cardiovascular risk factors, as defined by the AHA/ACCF, provided 75% sensitivity and 60% specificity for detection of severe CAD, as demonstrated in the ROC curves shown below (Figure 1.12). The authors also found that having ≥3 risk factors denoted a significant hazard risk of cardiovascular mortality (149). In this regard, traditional cardiovascular risk factors have continued to cement their place as a key component of cardiovascular risk assessment in LT candidates. Each of these risk factors will be discussed in further detail below, in addition to the changes in these risk factors post-transplantation.

Figure 1.12: Value of the sum of AHA/ACCF risk factors in predicting CAD among LT candidates, reproduced from reference (149) AUC, area under the curve; CAD, coronary artery disease

Post-transplantation, the cardiovascular risk profile for LT candidates is augmented further by the prevalence of metabolic syndrome which occurs in over 50% of patients after transplant (153). Most immunosuppression, in particular moderate to high dose steroids, contribute to worsening metabolic profile, and accelerated atherosclerosis (88). These factors culminate in significant mortality and morbidity from CVD in both early and late post-transplant recipients (154). The pathophysiology of post-transplant metabolic complications due to immunosuppression is summarised in Figure 1.13. Both traditional and non-traditional cardiovascular risk factors will be explored below, including the recommended management for each condition in the context of LT. A recent prospective study focused on the impact of a multidisciplinary intervention in reducing CAD risk post LT. The intervention group were provided with comprehensive, regular and multidisciplinary education to improve both lifestyle and pharmacologic management of CAD risk factors and compared with a control group with standard care (154). At 2 years post-intervention, there was a difference in incidence of CAD of 6% compared to 14% in the control group, trending towards significance (p =

0.063) (154). While this difference did not achieve statistical significance, it highlights the need for ongoing multi-disciplinary care for LT recipients.

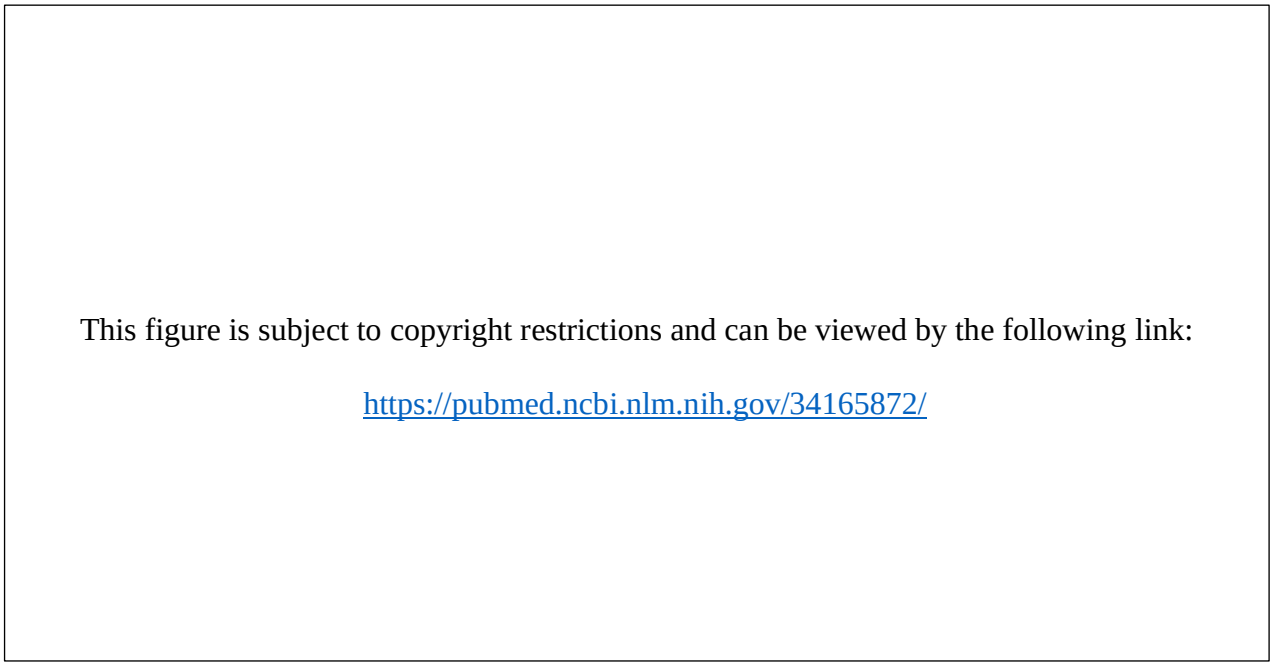

Figure 1.13: Pathogenesis of metabolic complications in the setting of immunosuppression, reproduced from reference (155). CNI, calcineurin inhibitors; mTOR, mammalian target of rapamycin.

1.9.3.1 Age

There has been an increase in the mean age of LT candidates worldwide. Among Australian LT candidates, the mean (± SD) age rose significantly from 44 (± 12) years in the 1980s to 52 (± 11) years in the 2010s (2). LT for patients above the age of 65 years has also increased, comprising up to 20% of LT candidates across the United States of America and up to 16% of LT candidates in Europe (6). All-cause LT mortality has improved over this time with better surgical techniques, effective antimicrobial protocols and better immunosuppression. However, with the inclusion of older LT candidates, the subset of patients >60 years does not appear to benefit as greatly from LT. This was

exemplified in an American population study of LT recipient age and mortality outcomes, where 5-year survival was 10 to 20% lower in LT patients aged ≥60–70 years (6).

In the most recent consensus guidelines from the Spanish Society of Liver Transplantation, the recommendations regarding age of LT candidates agreed that while age <70 years for consideration of LT is the standard of care, age alone should not be a formal contraindication (156). Those aged 70–75 years should have exhaustive evaluation for LT suitability, particularly for CVD and occult malignancy. These guidelines accept the relative reduction in benefit seen to those older LT candidates, provided it is balanced by minimal non-cardiac comorbidities.

1.9.3.2 MAFLD

There has been a shift in indications for transplantation over the past decade worldwide. Direct-acting antivirals have resulted in a reduced number of patients with hepatitis C referred for transplantation. However, there has been a rise in referrals for patients with MAFLD, hepatocellular cancer and alcoholic liver disease (27). MAFLD is strongly associated with obstructive CAD as shown in a prevalence study of CVD in LT candidates (OR 3.12, 95% CI 1.33-5.32), independent of other traditional risk factors for CVD (9). A recent prospective study from Korea reported a significant association between advanced liver fibrosis (using elastography) and development of CAD and stroke in type 2 diabetes development ($p < 0.001$) (157). A meta-analysis of 16 observational studies of MAFLD and CVD found that advanced MAFLD was associated with cardiovascular events, independent of the presence of other cardiovascular risk factors (OR 2.58, 95% CI 1.78-3.75) (158). In a further meta-analysis, MAFLD was associated with an increased risk of new-onset heart failure with a pooled hazard ratio of 1.5 ($p<0.001$), also independent of other cardiovascular risk factors (159). Furthermore, a meta-analysis of MAFLD and heart failure showed that worsening severity of

MAFLD had a cumulative increase in risk of new onset heart failure (159). In terms of the exact pathophysiology, the elevated risk of coronary atherosclerosis is related to hepatic fibrosis being a pro-inflammatory state with markedly elevated levels of pro-atherogenic mediators and chronic, refractory systemic microvascular inflammation (157). Further analysis of exact pathophysiologic mechanisms of MAFLD causing CVD has been explored using animal studies. A recent evaluation of metabolomics in MAFLD has found three metabolomic subgroups with each signature aligning with a different cardiovascular risk profile (160). Martinez-Arranz et al. studied mice lipid secretion in the setting of MAFLD, finding that mice with impaired very-low density lipoprotein secretion were associated with a slight attenuation in their cardiovascular risk profile, compared to mice with normal release of lipids (160). This suggests that the exact risk of CAD with MAFLD is heterogeneous and requires further quantification to guide risk.

Although it is considered a non-traditional cardiovascular risk factor, current evidence supports the recognition of MAFLD in the cardiovascular risk assessment for LT candidates. Patel et al. performed a prospective study of 341 candidates that underwent LT assessment at their transplant centre, where coronary angiography (CA) was a standard part of LT assessment for patients over 50 years of age (9). They found CAD was most prevalent in MAFLD cirrhosis patients, with MAFLD remaining a significant predictor of CAD after adjusting for age, gender, BMI, smoking, and family history of CAD (adjusted OR 3.1, 95% CI 1.3-5.3, $p = 0.005$). Interestingly, a recent 10-year retrospective analysis revealed an unexpected finding, with lean or normal BMI MAFLD patients shown to consistently have significantly higher rates of CAD ($p<0.01$) and stroke ($p<0.001$) compared to patients with obese MAFLD (161). This study suggests that BMI alone is inadequate to predict cardiovascular risk in the setting of MAFLD.

Following transplantation, weight gain, immunosuppression and post-transplant diabetes contribute to the development of *de novo* MAFLD (reported rates of 40-70%), in addition to the recurrence of MAFLD (reported rates of 57-82%) (162). Albeldawi et al. demonstrated that MAFLD LT recipients had increased post-transplant CVD compared to non-MAFLD patients (163). This highlights the need for continued aggressive risk factor management in the post-transplant population (154).

1.9.3.3 Systemic Hypertension

Systemic hypertension may not be evident in LT candidates with decompensated cirrhosis due to the presence of portal hypertension that leads to systemic vasodilation. It is important to look for the reversal of this phenomenon and hence hypertension as a treatment issue in the early post-transplant phase. Post-transplant, the blood pressure targets in the context of diagnosed hypertension are similar to the general population: <140/<90mmHg or <130/<80mmHg in the presence of DM (164). A retrospective study predicted that 92% of LT recipients will develop hypertension in the six years following transplant (164). Potential mechanisms of hypertension post-transplant include increasing age, calcineurin inhibitor (CNI) use and other immunosuppression drugs, and CKD. A recent comprehensive review suggested that non-pharmacologic treatments should be implemented first in all LT recipients with hypertension (144). This includes exercise, weight loss of 5% of total body weight, dietary salt restriction to 5g/day, and cessation of tobacco smoking (144). Calcium channel blockers are advised as they neutralise the vasoconstrictive effects of CNIs and are considered reasonable first-line agents in patients without other cardiovascular risk factors (155). Other therapeutic options include angiotensin converting enzyme inhibitors and angiotensin receptor blockers. These agents are routinely used in the setting of CVD and mild to moderate CKD to prevent myocardial remodelling and progression of renal failure (35). Potential adverse effects include hyperkalaemia, hypotension, and functional renal insufficiency, after years of use (165).

1.9.3.4 Type 2 DM

DM is an established predictor of CAD, including cardiovascular mortality in the general population. This also applies to the LT population and has been demonstrated in large studies of CVD and LT outcomes. Koshy et al. showed that pre-transplant DM is an independent predictor of post-transplant sudden cardiac death (166). The American Society of Transplantation consensus recommendations recognise the significance of DM by giving it the weighting of two cardiovascular risk factors and indicating that the presence of DM alone necessitates non-invasive testing for latent CAD (33).

A formal diagnosis of new onset DM post-transplant is made when hyperglycaemia persists >45 days post-transplant (163). Roccaro et al. found that incidence of major cardiovascular events was highest in those who developed new onset DM post-transplant, rather than pre-transplant DM (167). New onset diabetes after LT is also associated with renal and allograft dysfunction, in addition to a higher incidence of post-operative bacterial infections (163). New onset DM post-transplant has also been associated with worse survival compared to non-diabetic counterparts in multiple studies (168, 169). Risk factors for persistent DM post-transplant are exacerbated in the context of CNI use (particularly tacrolimus). Early referral for endocrinology advice and patient education are vital in preventing accelerated atherosclerosis and other end-organ complications of diabetes. The management principles of DM post-transplant are similar to that of the general population, and a recent review summarised the principles of management including target Hba1c <7%, annual screening for retinopathy and proteinuria, and utilisation of oral hypoglycaemic agents according to usual treatment algorithms (163). The use of sodium-glucose co-transporter-2 (SGLT2) inhibitors may pose a risk of volume depletion and genitourinary infection, according to the International Liver Transplant Society (170). While it may be prudent to avoid these agents in the early post-transplant period, safety of

SGLT2 inhibitors has not been studied in the post-transplant population. Given the prevalence of sub-optimally controlled post-transplant DM (up to 30%) (171), it seems prudent to use SGLT2 inhibitors, an oral medication with potential renal and cardioprotective effects. In a recent comprehensive review, Izzy et al. advocated for both SGLT2 inhibitors and glycogen like peptide 1 (GLP-1) analogues as first-line diabetes therapies given their cardioprotective effects (144). Furthermore, the AHA primary prevention guidelines strongly recommend the use of statins in all patients with DM who are also ≥40 years or in the context of other cardiovascular risk factors (172). In the LT population, this practice is heavily underutilised and should be encouraged routinely .

1.9.3.5 Chronic kidney disease (CKD)

Both albuminuria and reduction in eGFR are independent risk factors for CAD (173). End-stage renal failure is not considered a contraindication for LT, given the feasibility of simultaneous liver-kidney transplantation. Among LT candidates, CKD (in addition to MAFLD) is associated with a higher burden of CAD and more critical coronary stenosis (174). Early identification of CKD and prevention of further deterioration of renal function through treatment of the renal pathology when possible, and avoidance of nephrotoxins (nephrotoxic drugs, iodine contrast, and minimisation of calcineurin inhibitors) should be given priority in LT candidates (144). CKD continues to contribute to excess risk of CVD, reduced graft function and patient survival post-transplantation as demonstrated in a retrospective audit of over 400 patients (175). In particular, persistence of renal dysfunction at six months post-transplant appears to be predictive of coronary events and requires close follow up and risk factor management (176).

1.9.3.6 Dyslipidaemia

There is an increasing prevalence of metabolic syndrome in LT candidates due to the increasing prevalence of MAFLD, which persists in the post-transplant period (154). A cross-sectional study from Brazil found that by three years post-transplant, 50% of LT recipients developed metabolic syndrome (177). Dyslipidaemia makes up two of the diagnostic criteria for metabolic syndrome (hypertriglyceridemia and low levels of high-density lipoprotein), with the other three criteria being central obesity, hypertension and hyperglycaemia as manifestations of metabolic dysfunction and insulin resistance (177). Treatment of dyslipidaemia with low dose statin in the setting of cirrhosis is supported by evidence that statins are in fact beneficial through the reduction of hepatic fibrogenesis, the anti-tumour effects in the setting of hepatocellular carcinoma, and the protective effects against complications of portal hypertension (178). Previous hesitation about statin use in cirrhosis was related to the risk of statin-induced liver injury. However, given these events are typically idiosyncratic, statin therapy should be continued in cirrhosis if indicated.

Following transplantation, the importance of treating dyslipidaemia was demonstrated in a retrospective study of 500 LT recipients with a high prevalence of post-transplant dyslipidaemia (40-66%) (179). While statins were underutilised, a survival benefit was seen in patients appropriately prescribed statin therapy post-transplant (HR 0.25, 95% CI 0.12-0.49) (180). The development of post-transplant dyslipidaemia is further augmented by metabolic adverse effects of immunosuppression (sirolimus and cyclosporin more so than tacrolimus) and post-transplant diabetes (155). The choice of statin agent should be guided by potency and minimising drug interactions (173). Traditionally, pravastatin and fluvastatin (hydrophilic and low-potency agents) were used due to lower the risk of drug interactions, as most other statins are metabolised through cytochrome P450-3A4 causing a potential reduction in CNI level (163). However, even high-intensity statins such as

atorvastatin have not demonstrated clinically significant drug interactions with immunosuppressive agents in other organ transplants (181). While further studies are needed in the LT cohort, initiation and up-titration of statin should be prescribed when clinically indicated and paired with close monitoring of CNI levels. VanWagner et al. has further proposed that post-transplant guidelines adopt low cholesterol targets equivalent to patients with known CAD, in addition to guidance regarding drug-drug interactions with immunosuppression (182).

1.9.3.7 Pre-existing CAD

Traditionally, cirrhosis was not considered to be a risk factor for CAD as the coagulopathic state was thought to prevent atherosclerotic plaque accidents (183). However, prevalence of CAD in LT candidates is increasing, with a demonstrated prevalence of nearly 25% of LT candidates (184). Indeed, cirrhotic patients with MAFLD or renal impairment are at high risk of CAD, specifically critical CAD (33). A recent meta-analysis of over 16,000 LT candidates and systematic review of CAD found an association between pre-transplant CAD and both overall (OR 1.4; 95% CI, 1.4-1.4; P = 0.01) and cardiac related mortality (OR, 1.2; 95% CI, 1.1-1.3; P = 0.03) respectively (150). On the other hand, two recent single centre studies where patients only proceeded to LT after revascularisation demonstrated similar post-transplant mortality in patients with or without CAD (9, 152). Thus the explanation for these findings is that CAD continues to be prevalent in LT recipients, and adequate pre-transplant investigation and treatment is crucial to positive post-transplant outcomes. Therefore, the resources needed for anatomic assessment of coronary arteries in high-risk LT candidates is justified to allow appropriate treatment of coronary disease. This may permit patients to proceed to LT who may have otherwise been precluded, despite the potential for increased post-transplant mortality, and may influence how aggressively metabolic syndrome is managed post-transplant(145). Nonetheless, in borderline LT candidates with advanced multi-organ dysfunction

and adherence concerns, accurate identification of significant CAD may also serve to preclude transplantation where it is deemed unsuitable in improving a patient's overall longevity and quality of life.

Despite normal stress testing and addressing cardiovascular risk factors prior to transplant, some patients develop myocardial ischaemia in the setting of multiple cardiovascular risk factors in the peri and post-operative phase of LT. Microvascular coronary artery dysfunction has become an increasingly popular disease entity, particularly for patients with MAFLD, which is a known risk factor for microvascular myocardial dysfunction (97). Even invasive angiography is limited in its ability to diagnose coronary microvascular dysfunction, and thus optimising cardiovascular risk factors is the mainstay of treatment. This is of particular importance as the chronic inflammatory state present in HRS and CCM are risk factors for the development of coronary microvascular dysfunction and cardiac failure, thus leading to post-transplant CVD (185).

1.9.3.8 Obesity

Improved well-being associated with normal liver function after LT results in post-transplant weight gain. Corticosteroid use further contributes to increased appetite and weight gain (143). Additionally, alcohol use disorder, family history of obesity, smoking and male gender have also been associated with increasing obesity post-transplant (186). The 5 year post-transplant morbidity and mortality has been demonstrated to be higher in obese (body mass index, BMI, >40kg/m^2) than non-obese LT recipients in a meta-analysis of 24 studies (187). In essence, increasing BMI is inversely associated with adverse long-term patient survival in the setting of LT (186). Conflictingly, another registry study found no correlation between adverse survival and obesity at the time of LT (188).

Although the International Liver Transplant Society consensus statement states that obesity alone is not a contraindication for consideration of LT, the BMI cut-off in LT candidates remains controversial. However, if the underlying cause of liver disease is suspected to be MAFLD, addressing lifestyle factors that contributed to the class III obesity should be imperative to prevent MAFLD occurring in the new liver allograft. A detailed review of comorbidities is recommended in the presence of extremely elevated BMI prior to LT consideration (163). Bariatric surgery (sleeve gastrectomy) at or after LT should be explored in these patients (163). GLP-1 analogues are being increasingly utilised in the general population for weight loss in Australia. There is no data available on the safety of pharmacologic agents for weight loss post-transplant, nor that of endoscopic bariatric procedures, although they remain areas of active interest (189).

1.9.3.9 Cigarette smoking

Cigarette smoking is a recognised risk factor for CVD, based on observational studies. Smoking is responsible for 20% of CVD related mortality (190). Smoking cessation correlates with a relative reduction in CVD mortality within 5 years of current smokers (190). In the setting of MAFLD, cigarette smoking has also demonstrated a dose-dependent correlation with progression of liver disease (191). Treatment of nicotine addiction and smoking cessation is strongly encouraged pre-transplant, particularly given its association with adverse post-transplant outcomes (173). Tobacco use is not considered an absolute contraindication to LT in Australia, as per national guidelines from the Transplant Society of Australia and New Zealand. Nevertheless, abstinence is recommended and taken into consideration as part of the general LT assessment process. A meta-analysis published in 2017 found insufficient evidence to correlate cigarette smoking with worse post-transplant survival, however, LT recipients that smoke were found to have significantly higher rates of CAD and malignancy (192). Recidivism with regard to cigarette smoking post-transplant should be monitored,

and patients given the resources to manage and cease cigarette smoking, including nicotine replacement therapy, psychology services and pharmacologic anti-craving therapy.

1.9.4 Management of cardiovascular risk factors post-transplantation

Sastre et al. demonstrated in their prospective study that the best cardiovascular outcomes in LT recipients required a multidisciplinary approach (154). Educational sessions were targeted according to the number of cardiovascular risk factors present in addition to regular endocrinologist review, with 126 patients surviving to 12 months post-transplantation. Pharmacotherapy for hypertension and dyslipidaemia was increased in the intervention group, in addition to significant reduction in active smokers. At 12 months post-transplantation there was a trend to reduced CAD in the intervention group without reaching significance (154). Impacts of such intervention would be more demonstrable over years rather than months. The management targets of post-transplant cardiovascular risk factors with recommendation updates are summarised in Table 1.2 (154). Prospective studies of SGLT2 inhibitor use are needed in the LT population to confirm their safety and tolerability (193).

With regard to obesity and MAFLD, this is a particularly prominent issue post-transplantation. Multidisciplinary input is needed for dietary modification, regular physical activity and behavioural management to result in sustainable weight loss. More funding is advised to provide dietary consultation and exercise physiology input to those patients at risk of morbid obesity, thereby limiting the number of patients who require bariatric surgery and any associated complications.

Table 1.2: Cardiovascular risk factor management post-transplantation

Hyperglycemia	
Steroid induced hyperglycaemia	Insulin first-line as safer with weaning steroids
Therapies	Metformin (if tolerated and eGFR <30 ml/min/1.73m2) Second line: GLP1 agonist, SGLT2 inhibitor for those with renal or cardiac disease
Treatment targets (144)	Hba1c <7% in patients <75 years without severe comorbidities Hab1c 7.5-8.5% if prolonged diabetes or presence of complications Endocrine referral if poorly controlled or limited suitable therapies
Dyslipidaemia	
Therapies	Statins in all patients with DM age >40 years Low dose rosuvastatin or atorvastatin Ezetimibe second line Fibrates for those with hypertriglyceridaemia
Treatment targets	LDL <2 or <1.8 if established CVD
Systemic hypertension	
Therapies	First-line: dihydropyridine calcium channel blockers (amlodipine or nifedipine). Diabetes and/or proteinuria, ACE/ARB inhibitors first-line Second line: beta blockers, diuretics (thiazides)
Treatment targets (144)	BP <140/90 mmHg In diabetic patients <80 years-old: BP<130/80 mmHg

1.9.5 Surveillance of CVD post-transplant

The current recommendations for surveillance and management of CAD among LT recipients are similar to that of the general population. Investigations should be guided by suspected symptoms of angina, and there is limited evidence to support routine screening (144). Prospective, multi-centre studies of cardiac risk scores are needed to validate cardiovascular scores (such as the PROCAM score) in the LT population and guide whether MAFLD cirrhosis patients need more intensive surveillance. The CAR-OLT score (which must be done *post*-transplant) can be calculated to guide

risk of early post-transplant CVD (82). There is limited evidence for, or against, the use of aspirin as primary prophylaxis in the LT population (144).

1.10 Cardiac workup of LT candidates

1.10.1 Guidelines for CVD in LT candidates

Screening for CVD remains a major aspect in the workup of LT candidates and it is a predictor of adverse post-transplant outcomes (77, 119, 150). CAD is the most common form of CVD in the general population, therefore making it a crucial aspect of the pre-transplant workup.

Cardiovascular assessment in LT candidates begins with medical history and examination for signs and symptoms of CVD (22). Lentine et al. highlighted that the hyperdynamic circulation could mask cardiac symptoms in the setting of decompensated cirrhosis, and those with multiple risk factors need thorough evaluation for CAD (194). Cardiac investigations vary significantly across transplant centres and continents, resulting in heterogeneity among studies (150). The 2012 AHA/ACCF recommended the presence of at least 3 traditional cardiovascular risk factors to guide whether non-invasive cardiac stress testing is indicated pre-transplantation (194). These recommendations are reflected in guidelines, including the American Association for the Study of Liver Diseases (AASLD) guidelines for the evaluation of LT candidates (147). In 2016, the British Transplant Society presented further recommendations that patients with MAFLD cirrhosis undergo investigations for CAD, structural heart disease, and pulmonary hypertension, due to excess cardiovascular mortality in this cohort (195). Dobutamine stress echocardiography (DSE) is the most common cardiac stress testing modality due to its ease of access and lack of adverse complications (22). However, DSE relies on reaching maximal calculated heart rate in order conclusively assess for inducible regional wall motion abnormality to support functionally significant cardiac ischaemia. The sensitivity of DSE is hampered

by the use of beta blockers for variceal bleed prophylaxis, intercurrent illness and poor TTE images, all resulting in false negative, or inconclusive DSE studies (22). While coronary angiography (CA) is routinely performed in some transplant centres (196), this was discouraged in the AASLD and 2012 AHA/ACCF guidelines due to the risk of vascular complications and risk of renal impairment (22). The optimal screening method for CAD in LT candidates is less defined with the introduction of less invasive, and increasingly sensitive testing options available to patients. Furthermore, the issue of latent, asymptomatic CAD with moderate to severe coronary vessel stenosis continues to be an area of active investigation to guide when pre-transplant revascularisation is necessary (147).

Besides CAD, there is limited guidance provided by the AHA/ACC for management of structural heart disease in LT candidates. In 2018, comprehensive consensus guidelines were created by a working group in the US to address cardiac and pulmonary vascular disease assessment in LT candidates. Intensive care specialists, transplant surgeons, cardiologists and transplant hepatologists provided a group recommendation for the cardiovascular and pulmonary workup in LT candidates, as summarised in Figure 1.14. These guidelines give recommendations for all cardiac and pulmonary conditions and consensus recommendations for their management in the LT candidate (33). The benefit of these consensus recommendations is that it provides practical, specific scenario guidance with regard to suitability of LT. In particular, they highlighted that the procedural risk of CA in cirrhosis is lower than initial studies suggested (9). Furthermore, computed tomography coronary angiograms (CTCA) have become a popular means of accurate anatomic assessment of coronary arteries, with a lower risk than traditional CA (197).

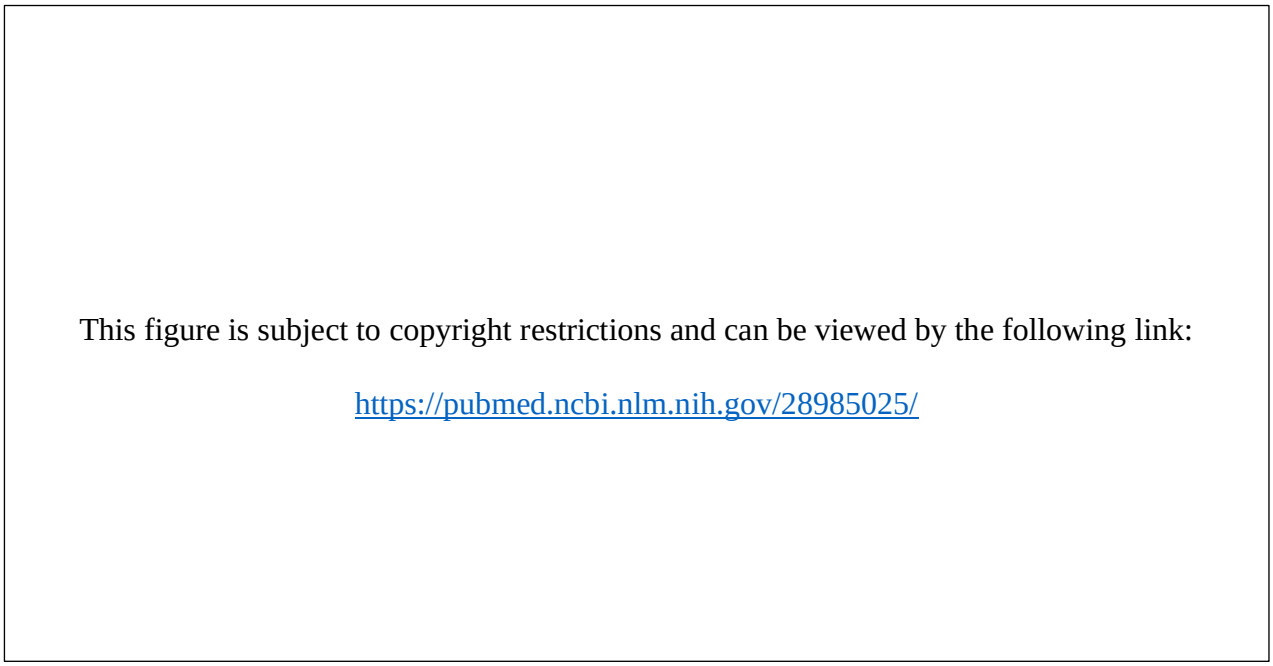

Figure 1.14: Cardiac contraindications to LT, reproduced from reference (33)

1.10.2 Cardiovascular risk stratification in LT candidates

Optimising cardiac workup for LT candidates is vital to improving both all-cause and cardiovascular morbidity and mortality post-transplant (88, 198). Literature review suggests that the strongest predictors of obstructive CAD in LT candidates are:

- Two or more traditional cardiovascular risk factors
- MAFLD
- Renal dysfunction

While pre-existing CAD is considered a traditional risk factor for future CAD, this risk is no longer considered prohibitive for LT provided appropriate revascularisation has occurred (152). A recent systematic review investigating the international variations in cardiac assessment of LT candidates highlighted that in 48.7% of transplant centres studied, cardiovascular risk factors were routinely considered in the investigational approach taken for CAD (150). This risk-based approach allows

rationalisation of resources, particularly for fragile cirrhotic patients at risk of complications from a procedure that in most cases is not necessary. Up to 10% of transplant centres, used CA as the standard of care for cardiac workup (150). Therefore, for those patients who have moderate-high risk of pre-existing or future CAD, utilising an accurate and efficient screening tool for latent CAD is vital for improving peri-operative and early post-transplant outcomes (88). In a prospective study, age and DM were given the greatest weighting to cardiovascular risk. High risk candidates (age >60 years, >50 years with DM, or re-transplant candidates) were prioritised for anatomic assessment of their coronary arteries using DSE and CTCA followed by CA, the gold standard for diagnosing CAD (88). At other LT centres, clinical risk stratification tools for CAD have been extrapolated to LT candidates, though not validated before in this population. For example, the traditional Revised Cardiac Risk Index (RCRI) uses 6 traditional risk factors to predict cardiac complications after non-cardiac surgery (including history of CAD, stroke, heart failure, diabetes, CKD and high-risk surgery). However, this tool is not specific to LT surgery nor cirrhotic patients (3).

The unique haemodynamic changes of cirrhosis, blood loss due to coagulopathy, electrolyte imbalance during reperfusion and the splanchnic congestion of portal hypertension pose unique challenges in LT surgery. Recently, Rachwan et al. created the first risk assessment tool to estimate the probability of significant CAD in LT candidates (198). Over 1700 LT candidates underwent cardiac evaluation and their clinical outcomes were analysed for predictors of abnormal stress imaging of the heart and abnormal CA results. They created the CAD-LT score using an odds-based scoring system, with the highest weighting given to personal history of CAD. The score is accessible on most smartphone devices via a downloadable app. The resultant risk score is shown below in the app format (available for free) with a reported sensitivity of 97%. By stratifying patients into low, intermediate or high risk, unnecessary delay in transplant workup is avoided. For example, a low-risk

patient requires only non-invasive testing, whereas a high-risk patient may need CA (198) (Figure 1.15). While promising, this risk score requires external validation to guide its utility and benefit before integration as a standard part of LT workup. Additional risk factors not included in this application include dyslipidaemia, however, accurate assessment of lipid status is frequently hindered by the dysfunctional homeostatic functions of cirrhosis.

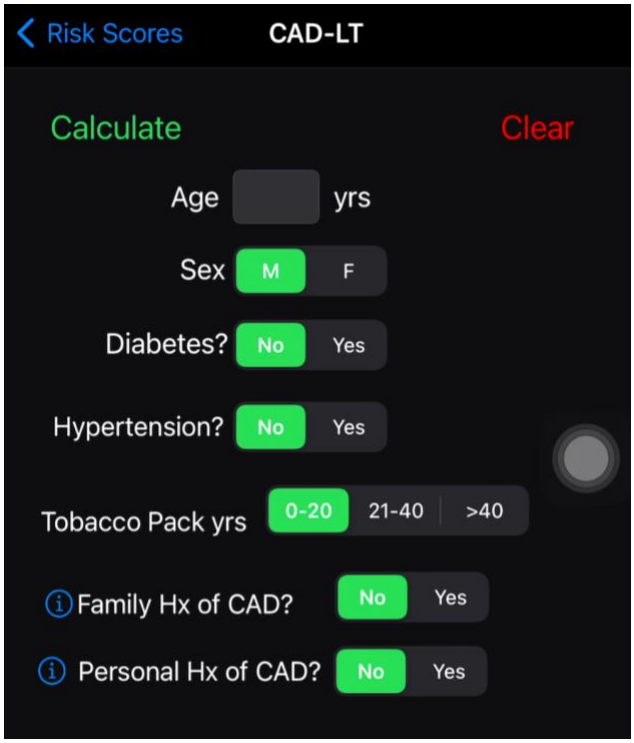

Figure 1.15: Screenshot of algorithm for CAD-LT score to predict risk and guide workup of CAD in LT candidates.

1.10.3 Dobutamine stress echocardiography (DSE)

DSE is the most commonly used functional imaging for LT candidates (89). The diagnostic endpoint for DSE includes achieving at least 80% of the age and gender predicted target heart rate (199). Its popularity as a screening test is due to ease of access, lack of radiation, and lack of contrast use. However, it is limited by inter-operator variability of interpreting echocardiograms, and the risk of

inconclusive findings if maximal heart rate is not achieved. The unique pathophysiologic changes of cirrhosis and portal hypertension resulting in the hyperdynamic circulatory state and inotropic incompetence also contributes to the poor sensitivity of DSE in the cirrhotic heart (89). Robertson et al. demonstrated the shortfalls of DSE in a prospective study of risk-stratified cardiac workup for LT candidates. All early post-transplant ischaemic coronary events that occurred in their patients were in those who underwent only DSE with no other anatomic assessment of their coronary arteries (88). Nicolau-Raducu et al. also found that DSE failed to identify patients at risk of early CAD events post-transplant in their cross-sectional analysis of LT recipients (7). Overall, a meta-analysis found that DSE had sensitivity of 25% and specificity of 68% for diagnosing CAD, and therefore a low positive predictive value in predicting risk of adverse peri-operative and post-operative outcomes (200). The poor sensitivity of DSE compared to other cardiac investigations for detection of latent CAD was further demonstrated in a recent comprehensive review (Figure 1.16) (201). No association was seen between positive DSE and intra operative or early post operative cardiac events (202). However, in those with CAD, abnormal DSE was associated with future adverse CVD (201). Therefore, DSE appears to be insufficient in predicting CVD and peri-operative risk in the setting of LT. The majority of transplant centres use a combination of anatomical and functional testing to diagnose CAD in LT candidates(150). Therefore, while the poor sensitivity of DSE is acknowledged, it remains an easy and simple screening method for low-risk LT candidates. Even with the introduction of more routine anatomic coronary artery testing, DSE and exercise stress echocardiography will continue to have a role in assessing the functional significance of underlying coronary artery disease. Furthermore, its role in the diagnosis of impaired myocardial reserve is also of prognostic significance for LT candidates and their risk of post-transplant myocardial dysfunction (70).

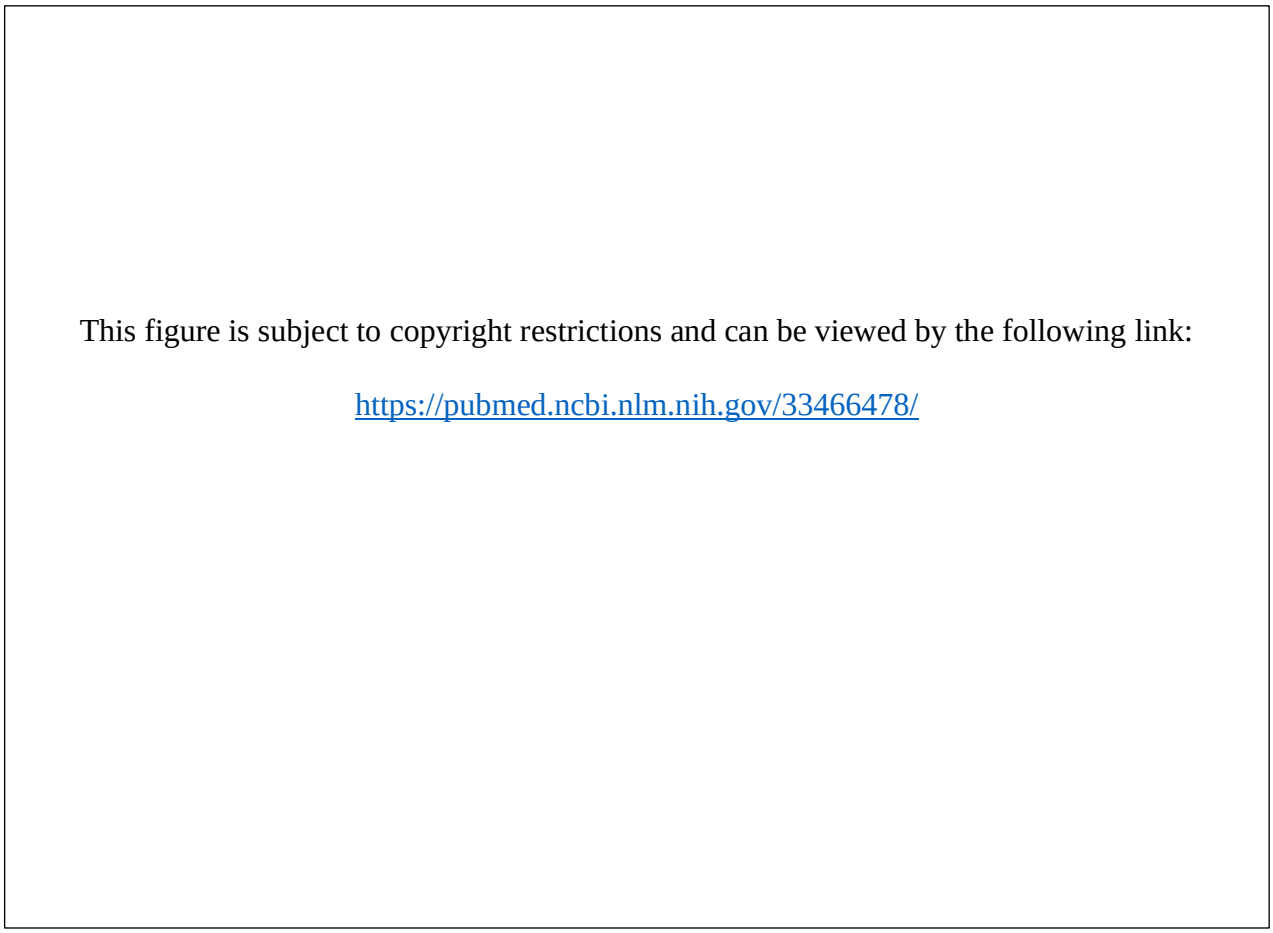

Figure 1.16: CAD assessment in LT candidates; reproduced from reference (201). Abbreviations: CA, coronary angiography; CACs, coronary artery calcium score; CAD, coronary artery disease; CCTA, computed tomography coronary angiography; CMR, cardiovascular magnetic resonance; CV, cardiovascular; DSE, dobutamine stress echocardiography; ESLD, end-stage liver disease; LV, left ventricle; GFR, glomerular filtration rate; MPI, myocardial perfusion imaging; NA, nonapplicable; NPV, negative predictive value; PPV, positive predictive value.

1.10.4 Nuclear medicine imaging

1.10.4.1 Myocardial Single Photon Emission Computed Tomography (SPECT)

Myocardial SPECT is a non-invasive modality used for the early detection of reversible myocardial ischaemia. During a SPECT myocardial perfusion scan, radiotracer is injected whilst a gamma

camera collects images. Impaired blood flow will reduce the tracer uptake into myocardium thereby detecting areas of significant ischaemia (203). Myocardial SPECT is usually performed at rest, and if no areas of ischaemia are seen, pharmacologic or exercise induced stress imaging is attempted. It has been used in the risk assessment of non-cardiac surgery, particularly for high risk surgery and in patients with poor functional capacity (203). Myocardial SPECT offers a slight increase in sensitivity and specificity compared to DSE. In the general population, SPECT myocardial imaging was found to have sensitivity of 71% and specificity of 67% for first order coronary artery branches (204). Among LT candidates, there are variable single centre studies with conflicting results regarding accuracy of myocardial SPECT for prognosticating future CVD events. There is also low sensitivity seen in myocardial SPECT with similar findings to DSE. Davidson et al. found a sensitivity of 37% and specificity of 63% for LT candidates screened with SPECT (205). Nicolau-Raducu et al. attempted to utilise SPECT imaging as an alternative to DSE in the cardiac workup of LT candidates for investigation of CAD (7). They showed that SPECT was not superior to DSE and resulted in a higher proportion of false negative results related to the presence of ascites affecting the attenuation at the inferior wall of the heart, diminishing its sensitivity (89, 206). Tiwari et al. performed a systematic review of DSE in comparison to nuclear medicine imaging in detection of CAD in LT candidates. Their study required patients to progress to the "gold standard" diagnostic test of CA, severely limiting the number of studies in each arm of analysis (207). Overall SPECT imaging does not appear to be superior to DSE due to the poor sensitivity for detecting significant CAD.

1.10.4.2 Positron Emission Tomography (PET) for myocardial perfusion scanning

Cardiac PET has not yet been studied widely in the cirrhotic population. PET should be explored in cirrhotic LT candidates given its lack of nephrotoxicity. Cardiac PET findings are also unaffected by the chronic, severe vasodilated state of cirrhosis. Current evidence for the safety and accuracy of

cardiac PET are derived from general population studies. In a prospective head-to-head study of CTCA with cardiac PET and SPECT in the general population, cardiac PET scans were found to have the highest diagnostic accuracy in detecting CAD (85%) compared to CTCA (74%) and SPECT (77%) imaging (208). A recently published retrospective study of different cardiac testing modalities in LT candidates found that cardiac PET was safe, and had a concordance rate of 87% when compared with those patients that proceeded to invasive CA (209). Further studies are needed into the role and accessibility of routine cardiac PET for screening of CAD in LT candidates.

1.10.5 Cardiac computed tomography (CT) CA

Non-invasive assessment for presence of CAD can be done using CTCA with or without coronary artery calcium scores. CT calcium score >400 is strongly associated with significant CAD (201). Reported risk factors associated with a high coronary calcium score include increasing age, male gender and DM. (210). Among LT candidates, CT calcium scores have been shown to predict cardiovascular complications early post-transplant. However, in those with multiple risk factors, it is insufficient for cardiac workup in the setting of LT, as these patients often require further investigation and revascularisation procedures (211). However, calcium scores can be rapidly estimated, non-invasive and carry low radiation. They also carry a higher positive predictive value than DSE in CAD risk (80% vs 56%) (212).

CT coronary angiography is a non-invasive means of anatomic assessment of the coronary arteries. (89). CTCA has the ability to take 300 trans-axial images at thin slices during a single breath hold, allowing for reconstruction of a 3D image of the heart (Figure 1.17) (213). Among the general population, it is one of the most valuable diagnostic tests for possible CAD. This is a low-radiation and low-contrast imaging modality that has shown 90% sensitivity, 40% specificity and accuracy in

detecting CAD among the general population. In the SCOT-HEART study, the investigation and management of patients with low-intermediate risk chest pain was randomised to either standard of care or standard of care plus CTCA (214). CTCA was found to improve the diagnostic accuracy of CAD (relative risk 1.79 95% CI 1.62-1.96 p <0.001), which at 5 years translated to a significant reduction in cardiovascular morbidity and mortality. While revascularisation rates were no different between CTCA and standard of care groups, the benefit seen in the CTCA group was attributed to increased utilisation and treatment of cardiovascular risk factors (214). There is an increasing trend to adopt CTCA into the diagnostic armamentarium for latent CAD in LT candidates. Löffler et al. conducted a prospective study of the presence and severity of CAD in LT candidates, documenting their experience with CTCA, CT calcium score, and CTCA with fractional flow reserve (215). Among 77 CTCA tests performed, 18 patients had moderate to severe luminal stenosis, however, the vast majority of this was diffuse and non-obstructive CAD. When high-risk disease (left main disease, three vessel disease or very high calcium score >1000) was found, this was the main trigger to proceed to revascularisation prior to LT. They argue that the very high sensitivity of CTCA is worth the resources, as it allows identification of patients who are at higher risk of adverse cardiovascular outcomes and patients who benefit from intensified primary prevention with regard to cardiovascular risk factors (215). While they did not describe any adverse events or complications associated with CTCA or CA use, their patient selection was highly restrictive, with estimated glomerular filtration cut-offs of <50mL/minute/1.73m^2 (215). Detection of even mild CAD using these advanced modalities pre-transplant is important. LT recipients are at risk of accelerated atherosclerosis, and less likely to form collaterals post-transplant (12). Accurately identifying these patients prior to transplant allows for more stringent cardiovascular risk factor optimisation.

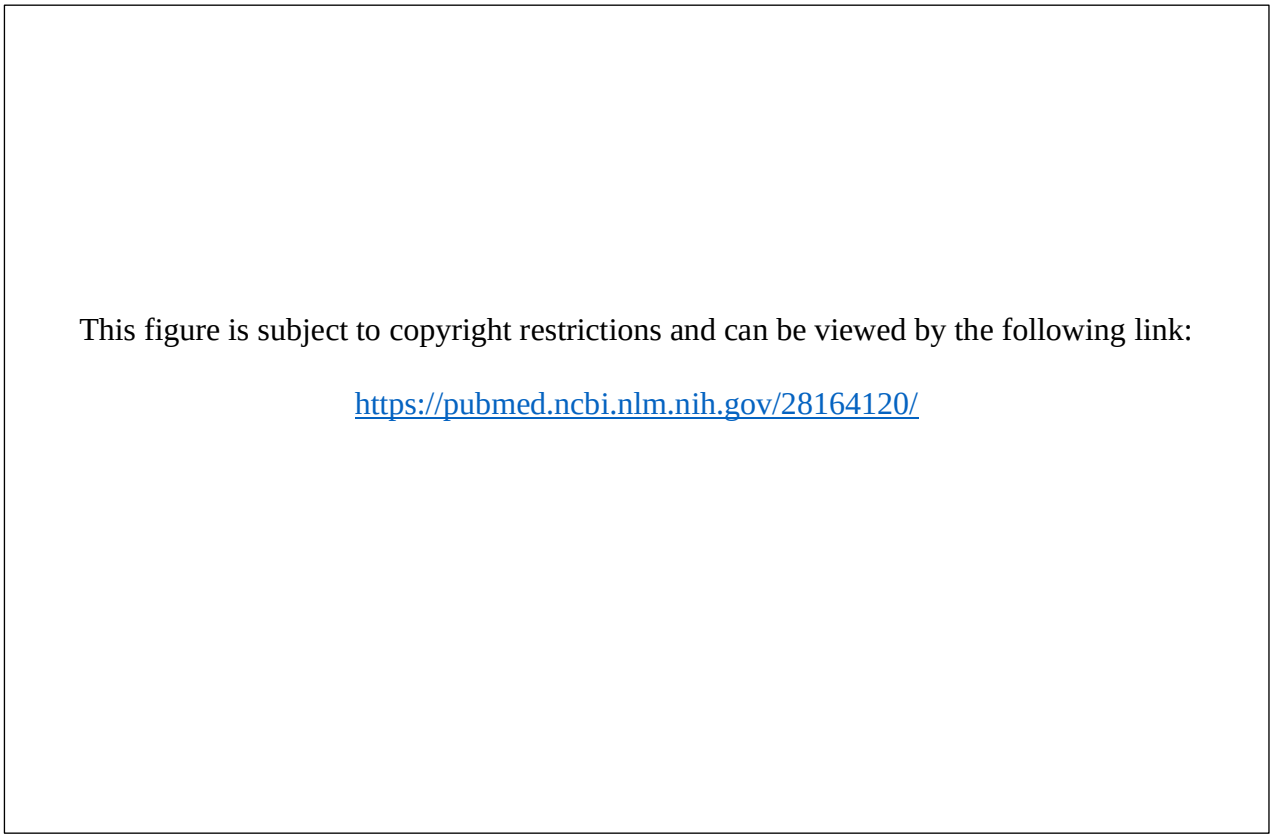

Figure 1.17: Three-dimensional volume-rendered images (a, c, e, g, and i) and angiographic images (b, d, f, h, and j) of the coronary artery obtained using computed tomographic angiography in patients undergoing liver transplantation. Arrows indicate coronary calcified plaques. A, aorta; B, left main coronary artery; C, left anterior descending artery; D, left circumflex artery; E, right coronary artery. Figure reproduced from reference (213)

There is limited evidence comparing CTCA to CA as an alternative method in LT candidates, however, given the high prevalence of non-obstructive CAD and mild multi-vessel atherosclerosis, CTCA is a promising modality that avoids the logistics and risks of traditional CA. The radiation dose of CTCA is lower than that of nuclear stress testing (197). CTCA also has lower risk of nephrotoxicity in comparison to invasive CA (89). CTCA has the ability to both reclassify patients as low risk of CAD with no further investigation, or higher risk prompting CA (216). CTCA has demonstrated a high negative predictive value of 91%, while its positive predictive value is hindered by factors such as tachycardia, diffuse coronary calcifications and severe renal impairment prohibiting contrast iodine use (201). The limitation from a logistic perspective is that it is a

specialised imaging tool, with limited number of personnel equipped to report the studies. Furthermore, patients should not be obese, need to be able to lie flat, and hold their breath for a brief period. Additionally, routine beta-blockade is given pre-procedure and so in patients intolerant to beta-blockade or patients with tachyarrhythmia, CTCA is contraindicated. In cirrhotic LT candidates with tense ascites and/or altered mental status due to hepatic encephalopathy, these factors may prevent acquisition of suitable images (213). Despite the downsides to CTCA, the safety, accuracy and feasibility of CTCA in LT assessment was recently demonstrated in a highly detailed prospective study of cardiac evaluation of LT candidates from the Victorian Liver Transplant Unit (88). Furthermore, in the setting of normal CTCA, a significant risk of post-transplant myocardial infarction can be safely excluded (217).

While CTCA is an excellent tool for excluding high risk atherosclerosis, it fails to recognise the hemodynamically significant lesion that can cause ischaemia despite modest luminal stenosis, with specificity of only 60% (208). Therefore, CTCA has the potential to overestimate the significance of any detected atherosclerosis. Since the addition of fractional flow reserve to CTCA, the functional significance of coronary lesions can also be assessed (201). Danad et al. studied the use of nuclear medicine imaging such as SPECT, cardiac PET in addition to CTCA and failed to demonstrate an improvement in diagnostic yield with these scans for determining whether a coronary lesion is hemodynamically significant. While these scans have better reported sensitivity than DSE (SPECT 62%, cardiac PET 89% compared to DSE 25%), the addition of fractional flow reserve (FFR) was superior in both sensitivity and specificity of detecting significant CAD in the LT candidate (89% and 92% respectively).

1.10.6 Coronary angiography

1.10.6.1 Rationale for CA

Pre-transplant CAD is a strong predictor of higher mortality post-transplant. Maddur et al. demonstrated that with increased frequency of CA and coronary intervention, regardless of DSE result, a reduction in all-cause mortality and MI rate was demonstrated among LT recipients (218). While CA is considered the gold standard for diagnosis of CAD, the majority of transplant centres use a combination of anatomical and functional testing to diagnose CAD in LT candidates (150). A recent North American consensus statement on cardiac workup of LT candidates agreed that CTCA +/- CA should become the standard of care in cardiac workup (89). Similar to CTCA, correlation of anatomical findings with FFR or DSE at the time of CA is necessary to decide on revascularisation of detected lesions. In a review of CAD in LT candidates, Hogan et al. recommended those LT candidates with ≥3 cardiovascular risk factors should directly undergo CA due to their excessive risk of underlying CAD (219). Patel et al. utilised a per protocol approach whereby all patients age >50 years or with traditional CAD risk factors underwent CA. They argued that reserving CA for those with abnormal imaging could induce a sampling bias, and that the risks of CA were minimal in cirrhotic patients (9). Notably, among this high-risk cohort they found the pre-transplant CAD prevalence was nearly 35%, with MAFLD the strongest independent predictor of CAD (9). While this study helped increase confidence in proceeding to CA, larger studies are needed regarding benefit of diagnosing non-obstructive coronary lesions in improving peri-operative or post-transplant outcomes.

1.10.6.2 Risks of CA in LT candidates

It is important to be aware of the risks of CA in the setting of decompensated cirrhosis (22). Potential complications include bleeding from procedure site, contrast-induced AKI, or procedure specific risks including severe arrhythmia, coronary dissection and death (90). However, the rates of post-CA

complications have plummeted since the introduction of the radial artery approach (9, 88). Using a trans-radial approach and minimising sheath size reduces the risks of CA in LT candidates to that comparable to the general population in several case series, with bleeding risk mitigated by thromboelastometry to guide blood product replacement (88, 89, 220). Prevention of contrast-related AKI is also advised by maintaining intravenous hydration and minimising contrast dye, however, studies of specific preventative strategies against contrast-induced nephropathy in cirrhosis have not been performed. Table 1.3 summarises the existing studies of CA in cirrhosis and prevalence of complications. Consultation with nephrology for prevention of contrast-induced nephropathy for at-risk patients with advanced CKD is also advised (33). Large volume cohort studies of various stages of cirrhosis demonstrate an acceptable procedural complication rate of 7% and mortality rate of 3.6% among cirrhotic patients (221). Overall, the improvements in procedural risk over the past 20 years is very encouraging, with the remaining risk related to post-procedural bleeding in the cirrhosis population (222).

Table 1.3: Safety of coronary angiography in LT candidates

	N	**Median MELD**	**Approach**	**Platelet count**	**INR**	**Transfusion requirement**	**Vascular complication**	**AKI**	**1 month survival**
Sharma et al. (183)	88	-	Femoral	90	1.6	14.8%	5.7%	-	-
Azarbal et al. (223)	16	13	Femoral	68	1.3	13%	0%	-	100%
Jacobs et al. (224)	82	19	Radial	74	1.4	7.3%	2.4%	2.4%	92%
Huded et al. (220)	71	21	Radial	75	1.7	4.2%	1.4%	0%	97%
Patel et al. (9)	228	15	Both	102	1.5	1.3%	0.9%	0.9%	100%
Koshy et al. (222)	16	16	Both	96	1.4	12.5%	0%	-	100%

1.10.6.3 Coronary revascularisation by PCI

In the setting of myocardial infarction, there is a mortality benefit to revascularisation and improvement in cardiac symptoms (225). For the general population with stable CAD, evidence of improved mortality or symptoms after revascularisation of stable CAD remains limited (226). The decision to explore revascularisation of CAD detected in LT candidates should be considered if the burden of coronary atherosclerosis is considered prohibitive to LT (33). Recent studies have demonstrated that irrespective of severity or extent of CAD, LT recipients have similar outcomes to those without CAD, emphasizing the importance of treating significant, asymptomatic CAD (7, 152). It is important to have a multidisciplinary discussion prior to revascularisation for the management

of significant detected lesions before CA is performed. The timing of revascularisation is crucial and should occur once the patient has already been deemed an acceptable transplant candidate (33).

There have been no head-to-head studies comparing percutaneous coronary intervention (PCI) to coronary artery bypass grafting (CABG) in LT candidates, particularly given the risk of CABG in decompensated cirrhosis remains significant. In the case of PCI, bare metal stents are recommended first-line, primarily to minimise the duration of dual antiplatelet therapy (33). Promisingly, the 3rd and 4th generation of drug-eluting stents (DES) are now routinely used for patients at high risk of bleeding as they require a shortened period of dual antiplatelet therapy to a minimum of 6 weeks in some cases, making them a favourable option moving forward despite the lack of data of these stents in advanced cirrhosis (33). LT candidates are to remain inactive on the LT waitlist during their time on dual antiplatelet therapy (22). Higher bleeding rates are predictably associated with dual antiplatelet therapy; however, the majority of this bleeding was related to peptic ulcer disease rather than variceal bleeding in one study, with this risk only becoming statistically significant at 1-year post-stenting (200). Koshy et al. describe two bleeding events in their post-PCI population who subsequently died on the LT waitlist, highlighting that the adoption of abbreviated time on dual antiplatelet therapy to one month with the DES allows for optimal revascularisation (222). The traditional thinking was that liver disease should drive the choice between bare metal stents and DES, however with shorter times on dual anti-platelet therapy allows for better revascularisation options for this high bleeding risk cohort (1).

1.10.6.4 Revascularisation by CABG

All stages of cirrhosis carry a higher mortality risk for any cardiac surgery compared to the general population, including CABG (227). Cirrhosis is associated with increased risk of multi-organ

dysfunction, increased hospital length of stay and severe post-operative infection, with recognised risk factors including advanced age, female gender, ascites and decompensated heart failure associated with the cardiac disease (33, 228). Patel et al. presented a mortality rate of 80% in LT candidates that undergo CABG, despite a median MELD score of 13 (9). If necessary, CABG may be undertaken for LT candidates, however, consensus guidelines advise appropriately selecting CABG candidates to optimise LT and survival outcomes (33). Recently, the VOCAL-PENN score has been increasingly as an externally validated tool in the setting of cirrhotic patients needing open surgery (229). It has become a useful adjunctive tool in predicting the risk of specific surgery types in cirrhosis, including risk of cardiac surgeries (229).

1.10.6.5 Functional cardiovascular testing

Functional cardiovascular testing is a known predictor of post-operative cardiovascular complications (202). The role of functional testing in the workup of LT candidates remains poorly defined and an area of active research in approaching the LT candidate who has evidence of deconditioning and frailty. The most commonly applied form of functional testing is the measurement of metabolic equivalent of tasks (METs) (22). Walking up two flights of stairs is equal to four METs of work, a common integer used to guide function and physiologic reserve in patients pre-operatively (195). Six-minute walk testing can be used to predict post-operative mortality risk in LT candidates (22). One study found that walking <250 metres predicted higher waitlist mortality (230).

Cardiopulmonary exercise testing (CPET) was recently introduced to improve assessment of frailty in LT candidates within SALTU. In addition to assessing exercise tolerance and aerobic capacity, CPET has the ability to assess cardiovascular and pulmonary performance in a functional capacity, to determine the specific cause of reduced cardiopulmonary reserve (33). CPET therefore has the

ability to assess the physiologic implication of any cardiac structural abnormalities that are detected and provide insight into the aetiology of a patient's physical limitations (231). A recent systematic review found that poor performance in CPET was an independent predictor of excess post-transplant mortality among LT recipients (232). However, performing CPET requires subspecialist input for interpretation and the equipment requires strict calibration, these requirements limit the accessibility to CPET (202). Furthermore, standardised cut-offs to predict adverse post-transplant mortality have yet to be defined (232). These factors pose barriers to frequent testing and their utility in the routine clinical setting (10).

1.10.7 Hepatopulmonary syndrome

Hepatopulmonary syndrome (HPS) is diagnosed as a triad of abnormal arterial oxygenation and intra-pulmonary vascular dilation in the setting of chronic liver disease (233). The pathophysiologic basis of HPS is poorly understood, with the current understanding being accumulated inflammatory cytokines and vasoactive mediators including COm and NO inducing pulmonary endothelial dysfunction with accelerated angiogenesis and subsequent shunt formation (233). Clinical manifestations often include clubbing, platypnoea, orthodeoxia and interstitial adventitious lung sounds (234). The diagnosis is usually made using micro-bubbles appearing after 3-5 cardiac cycles on TTE. Grading of severity of HPS is based on arterial blood gas results, whereby mild disease is $\geq$ 80 mmHg, moderate is 60-79 mmHg, severe is 50-59 mmHg (233). Overall, HPS remains uncommon, but important to recognize as pulmonary vascular condition that can impact cardiac function and patient survival. HPS carries a morbidity and mortality risk that can only be cured through LT. Very severe cases of HPS with arterial oxygen of < 50 mmHg usually confers excess mortality risk, including a prohibitive risk during LT surgery (233).

1.10.8 Portopulmonary hypertension

PPTHN is an uncommon complication in patients with cirrhosis, affecting 2-6% of patients with clinically significant portal hypertension (33). Screening for PPHTN occurs using TTE, and the diagnostic criteria relate to the parameters found on right heart catheterisation, including mean pulmonary arterial pressure greater than 25 mmHg, pulmonary vascular resistance greater than 240 dynes·sec·cm-5 and pulmonary arterial occlusion pressure less than or equal to 15 mmHg , with no other cause of pulmonary hypertension identified (127). PPHTN is a highly morbid condition due to the associated right heart failure.

There are certain factors that increase the risk of a missed diagnosis of PPHTN. In the absence of significant tricuspid regurgitation, an estimated PAP cannot be provided by screening TTE during LT workup, leading to a risk of missing significant pulmonary vascular disease (233). Recently, Raevens et al. proposed the addition of right ventricular dysfunction as a sensitive and specific finding of PPHTN, when ePAP cannot be estimated (233). A retrospective study of LT candidates in SALTU also found that PAP is influenced by severity of liver disease and hyperdynamic circulation and should be factored into the interpretation of screening TTE in LT candidates (235).

PPHTN can occur both in cirrhotic and non-cirrhotic causes of portal hypertension (236). Moderate (>35mmHg) PPHTN is associated with increased mortality but is potentially amenable to therapy, whereas severe (45mmHg) PPHTN is an absolute contraindication to LT due to severe mortality risk. Potential therapeutic options include oral phosphodiesterase five inhibitors, endothelin receptor antagonists and intravenous prostacyclins (33), which are often used in combination for improved outcomes. Reassessment of pulmonary pressures for response to medical therapy is a necessity for LT listing. A recent retrospective study found that while LT improved PPHTN, PPHTN was an

independent predictor of graft loss compared to patients without PPHTN (237). Furthermore, despite requiring a mPAP of <35mmHg and a PVR of <3 woods units to be listed for LT as per guidelines, a PVR ≥1.6 wood units was a strong predictor of survival in comparison to mPAP (adjusted HR 2.21, standard error 0.85, p = 0.02). PVR provides a better reflection of primary pulmonary vascular disease, while adjusting for increased cardiac flow in the setting of fluid overload. Thus PVR is a reliable surrogate marker in demonstrating response of PPHTN to vasodilator therapy and thus optimising post-transplant survival (233). In fact, given the existence of PPHTN in patients without cirrhosis, most contemporary guidelines emphasize the need for a primary hepatic indication for LT in order to be listed, *in addition* to a sufficient haemodynamic response in their pulmonary vascular disease to vasodilator therapies (33, 233). In conclusion, the consensus guidelines by VanWagner et al. adeptly surmise that given the complexity of PPHTN, multidisciplinary decision-making among cardiology, respiratory and anaesthesiology is necessary to determine LT suitability (33).

1.10.9 Valvular heart disease

Whether valvular heart disease occurs secondary to senile degeneration or a congenital malformation, the severity of the valvular pathology and its amenability to surgical repair is the crucial factor to determining LT suitability. Small studies have suggested that anything more than mild valvular dysfunction may confer adverse prognosis in LT candidates (144). Aortic stenosis is the most epidemiologically common valvular disease, and it is also the most well-studied valvular pathology in LT. While evidence of trans-catheter aortic valve replacement is limited, there are small studies with promising outcomes in LT candidates (33). Trans-catheter aortic valve replacement is better tolerated and similarly effective to surgical aortic valve repair. With regard to mitral and tricuspid regurgitation, ensuring that the valvular pathology remains suitable for surgical intervention allows progression to LT with review of valvular repair post-transplantation.

1.10.10 Arrhythmias

Arrhythmias can occur due to structural or functional cardiac abnormalities. They are the most common cardiovascular complication of the early peri-operative period. Risk factors include previous atrial fibrillation (AF), CAD and DM (144). AF is the most common arrhythmia found in LT candidates. AF has a reported prevalence of 1–6% in LT candidates, yet in the early post-operative period, up to 43% of LT recipients develop AF, often requiring hospitalisation (238). This high prevalence continues post-transplantation. AF is associated with adverse LT outcomes, which appears to occur independent of the use of anticoagulation (33). The presence of arrhythmias is not a contraindication to LT, however, investigating for different causes of CVD is necessary (33).

If AF is present, warfarin is the preferred anticoagulant used in LT candidates as it can be fully reversed and accurately monitored using the international normalised ratio (INR), particularly when patients are on the LT waitlist. Pre-transplant AF was the strongest predictor of post-transplant arrhythmia (OR 6.7, 95% CI 2-2.2, p <0.001) as shown by Rachwan et al. (4). Cox proportional hazard regression modelling confirmed that post-operative AF was also an independent risk factor for post-transplant mortality (OR 2.0, 95% CI 1.3-3.0, p <0.01) (4). Following transplantation, direct oral anticoagulants are preferred to warfarin due to less drug interactions and superior safety profile (144). The management algorithm for AF in the LT recipient is similar to that of the general population (144). However, given the growing body of literature highlighting the association between AF and adverse post-transplant outcomes (82), a better understanding of the management of arrhythmias in the post-transplant population is necessary.

The pathophysiology and importance of QT prolongation was covered in section 1.5.3.3. The significance of identifying and mitigating risk associated with QT prolongation was highlighted by Koshy et al., as the delayed ventricular repolarisation in the cirrhotic heart, coupled by the physiologic stress of the LT surgery, may exacerbate the underlying risk of cardiac arrest or ventricular arrhythmias that have been observed in LT recipients (108). These findings are in contrast to others that did not find a significant correlation between QTc and excess cardiac mortality (107, 239). While QTc was traditionally considered a finding that lacked clinical importance in the setting of decompensated liver failure, the substantial risk of cardiac arrest and ventricular arrhythmia associated with prolonged QT in recent studies necessitates further prospective studies in this area (108). Potential treatment options include avoidance of hypokalaemia, avoidance of QT-prolonging medication, and treatment with beta blockers (108). A detailed family history to support a true diagnosis of Long QT Syndrome is necessary in all patients with prolonged QTc (82).

1.11 Impact of CVD on LT outcomes

CVD remains a leading cause of mortality in the early post-transplant period, particularly with improvement in surgical technique and antimicrobial management. One of the largest population studies of post-transplant CVD found that heart failure was a leading cause of early post-transplant mortality, among over 50,000 LT recipients, with CVD accounting for up to 40% of post-transplant early mortality (within 1 year) despite all recipients undergoing pre-transplant cardiac workup (119). Furthermore, with the increasing age and prevalence of MAFLD, the individual cardiovascular and atherosclerotic risk of LT patients has increased over time (6). This has triggered increased scrutiny of the pre-transplant cardiac assessment and emphasis on management of post-transplant cardiovascular risk factors. Cases of post-transplant heart failure are increasingly recognised, and those with pre-transplant cardiac dysfunction (including CCM, PPHTN and pre-existing CVD) are

most susceptible to this complication (80). While some studies show encouraging evidence that CCM resolves within 6–12 months of LT, it can significantly impact cardiovascular reserve in the peri-transplant period (45). Physicians are therefore increasingly responsible for identifying patients with advanced cardiac dysfunction and closely following their post-transplant course.

1.11.1 Peri-operative cardiac complications

The rate of peri-operative severe arrhythmia or cardiac arrest in LT is over 4 times that of other non-cardiac surgeries (119, 240). This is likely attributed to the haemodynamic sequelae of advanced liver disease including inotropic incompetence, systemic vasodilation, and overload of the splanchnic system (43). The intra-operative fluid shifts in the setting of LT can be immense, particularly as the liver can carry 1.5–2 litres of blood volume at any given time. Thus, avoiding large fluid shifts in the setting of CCM and PPHTN is advised (125). Having anaesthesiologists with experience in LT surgeries and their risks is crucial to optimal surgical outcomes. The challenge of maintaining preload in the setting of cardiac dysfunction or coagulopathy has previously been advised as a key factor to maintain CO in this fragile population (89), however, this must be balanced with the risk of profound fluid overload. One of the earliest studies of cardiac arrest during LT surgery identified the cardiac arrest incidence rate of 5.5% with predictors of peri-operative cardiac arrest including post-reperfusion syndrome and thromboembolic events (241).

Immediately after release of the inferior vena cava, there is a rare risk of post-reperfusion syndrome. This phenomenon is defined as a decrease in mean arterial pressure of more than 30% for at least 1 minute, within the first 5 minutes of reperfusion of the liver allograft (89). Post-reperfusion syndrome can clinically be characterised as immediate cardiac arrest or severe arrhythmia at the time of blood influx into the right heart from the inferior vena cava (89). Post-reperfusion syndrome is exacerbated

by the substantial volumes of ischaemic metabolites and electrolyte imbalance in LT surgery. Post-reperfusion syndrome is estimated to have a prevalence rate of up to 30% (211). It is unclear whether pre-transplant CVD confers increased risk of post-reperfusion syndrome. These haemodynamic factors are unique to LT surgery and explains why extrapolating cardiac risk assessment scores from other forms of surgery may not necessarily apply to LT surgery.

Some of the other intraoperative cardiac complications of LT surgery include acute myocardial dysfunction and arrhythmia. One single centre study found that intra-operative blood transfusion of >11 units was associated with an increased risk of early post-transplant heart failure (121). The persistence of myocardial dysfunction (attributable to CCM or other causes), plus the added insult of LT and its complications, is theorised to contribute to cardiovascular collapse in the early post-operative setting. Immediately post-transplant, there is rapid improvement in portal hypertension, including an increase in systemic vascular resistance and mean arterial pressure (14). The prompt increase in venous return can elevate cardiac preload and precipitate acute heart failure (242). One case series demonstrated this with post-operative trans-oesophageal echocardiography in LT recipients in addition to daily TTE. In their LT centre they experienced three episodes of acute catastrophic cardiac failure immediately post-transplant despite only mild abnormality in pre-transplant echocardiograms (243). Having pre-transplant CAD has also been demonstrated to be a risk factor for adverse cardiac outcomes in the immediate post-transplant period (201). In the early post-transplant period, the utility of elevated BNP levels was supported by one case series as an early diagnostic tool of cardiac failure (244). Another retrospective analysis found the occurrence of peri-operative heart failure was an independent predictor of early mortality (OR 15.11, 95% CI 1.8-129.6) (93). Nevertheless, accurately identifying which LT candidates are at particular risk of cardiac decompensation continues to be a challenge.

1.11.2 Early post-transplant cardiovascular events

A recent review by Barman and VanWagner highlighted that approximately 1 in 3 LT recipients will experience a cardiovascular event in the first year following LT (89), contributing significantly to post-transplant healthcare costs. The reported incidence rates of post-transplant heart failure have ranged from 10–27%, the wide range is attributed to inclusion criteria and definition of heart failure used (92, 93, 120). In a study of major adverse cardiovascular events post-transplant, the incidence of post-transplant CVD (including both ischaemic and non-ischaemic events) was found to be 8% at 30 days and 11% at 90 days, with a predominance of non-ischaemic events such as heart failure or dysrhythmia (238). Early cardiac morbidity was associated with worse survival at 1-year, in addition to overall mortality (238, 245). The strongest predictors of early post-transplant CVD were atrial fibrillation and stroke with incidence rate ratios (IRR) of 6.9, 95% CI 5-9.6 and 6.3, 95% CI 1.6-25.4 respectively (238).

In a multicentre study of over 54,000 LT recipients, the all-cause early (within 30 days) mortality rate was 2.9%. CVD related mortality accounted for 42.1% of these deaths (119), surpassing both infection and graft failure. Nine significant predictors of early CVD mortality were found including age, hospitalisation status, ICU status, respiratory failure on a ventilator, MELD score, history of portal vein thrombosis, national organ sharing, donor BMI, and increased cold ischaemic time. The highest odds of CVD mortality was related to respiratory failure with an aOR of 2.05, 95% CI 1.5-2.9, $p < 0.001$ (119). These risk factors for CVD mortality are all related to increasingly comorbid LT candidates rather than the traditional risk factors for CAD. Evaluating allograft allocation to highly comorbid patients with poor functional status requires multidisciplinary review given the high prevalence of subclinical cardiac dysfunction in LT candidates (119). Similar conclusions were drawn

by an Australian research group that found comparable early cardiovascular mortality rates to the American population despite an overall reduction in post-transplant mortality (2).

The Victorian LT unit recently performed a comprehensive assessment of the risk factors associated with adverse peri-operative cardiovascular events and their impact on long-term post-transplant outcomes. Among 319 LT recipients, 23.2% of LT recipients experienced a cardiovascular event within 30 days of LT (76). Identified predictive factors included CCM, HRS, PPHTN, poor functional status and beta blocker use, with no association found with the presence of traditional cardiovascular risk factors or severity of liver disease (76) (Figure 1.18). The implication of CCM on the pathogenesis of HRS has already been discussed. However, the novel finding that HRS is an independent predictor of post-transplant CVD has the potential to transform the management of HRS in LT candidates, encouraging increased vigilance for CVD in the early post-transplant period.

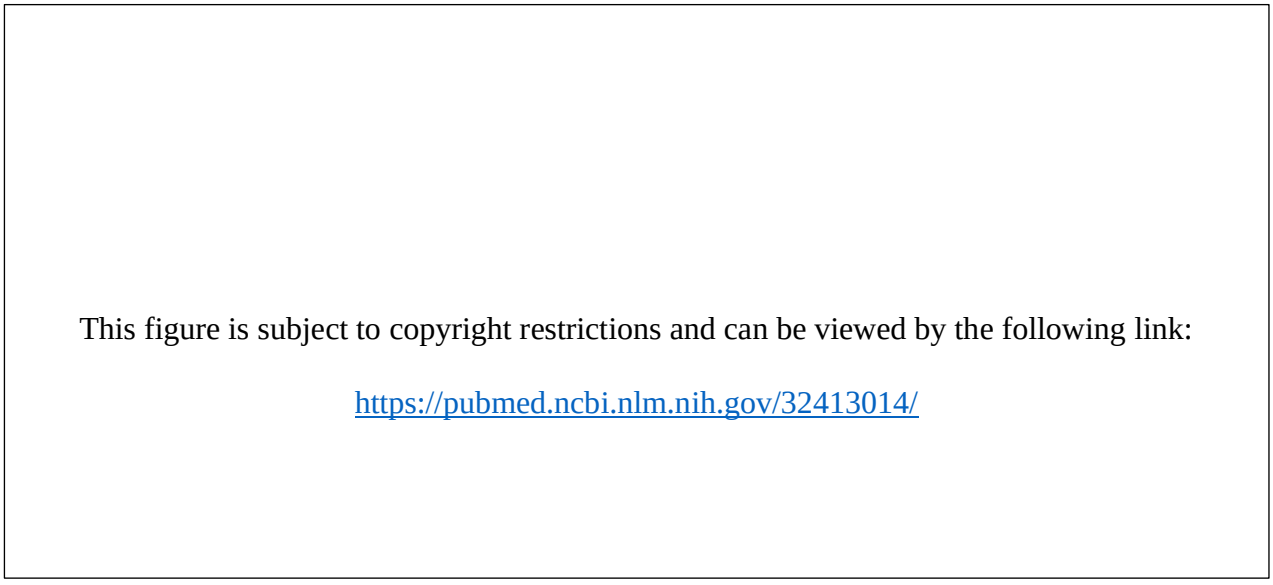

Figure 1.18: Predictors of major adverse cardiovascular events at 30 days post-transplant. Reproduced from reference (76)

Eimer et al. reported advanced age and higher intra-operative pulmonary artery pressures to be predictors of post-transplant heart failure in their description of the outcomes and predictors of severe heart failure post-transplant (246). Eyvazian et al. found that 11% of their post-transplant cohort developed heart failure with reduced EF (<40%) by six months post-transplant and they had wall motion abnormalities on pre-transplant echocardiograms predictive of post-transplant heart failure. Post-transplant heart failure was a predictor of adverse mortality (247). Izzy et al. demonstrated a trend towards the development of heart failure in the first 90 days post-transplant in patients diagnosed with CCM pre-transplant ($p = 0.086$) (80). Koshy et al. described the Australian experience in early cardiovascular events post-transplant, finding a predominance of arrhythmia, heart failure and cardiac arrest as the major adverse cardiovascular events in the early post-transplant period (76). Nicolau-Raducu et al. reported a prevalence rate of 5.4% of ischaemic coronary events occurred in in the first 10 days post-transplant, and that those with two or more traditional cardiovascular risk factors were at highest risk of early post-transplant CAD (7). The higher prevalence of early post-transplant ischaemic events in this cohort occurred despite standard cardiac workup, utilising DSE as the screening method in their centre (238). Satapathy et al. and Wray et al. also found that while early CAD events occurred post-transplant in those with pre-transplant CAD, there was no significant impact on survival, provided appropriate revascularisation occurred (7, 152, 248). Potential mechanisms responsible for early post-transplant ischaemic myocardial injury include an accumulation of large haemodynamic shifts, rupture of soft plaque, and pre-transplant subclinical cardiomyopathy (7).

1.11.3 Late post-transplant cardiovascular morbidity and mortality

Owing to the evolving profile of older LT recipients, there is an increase in the frequency and severity of cardiovascular events in the long-term. Furthermore, certain post-transplant factors including

increased prevalence of hypertension, DM and increasing age in the context of long-term immunosuppression, particularly with CNI therapy contribute to a reported 40% increase of metabolic syndrome prevalence (249). A retrospective study found that the prevalence of de novo post-transplant CAD was 30% by 8 years after LT (151). The prevalence of metabolic syndrome is also steadily increasing in the post-transplant population, further precipitating the prevalence of CAD in LT recipients. Fussner et al. found that up to 50% of LT recipients developed post-transplant metabolic syndrome (closely correlated with the presence of post-transplant MAFLD), despite only 10% of LT recipients having MAFLD as the initial LT indication (151). This may be due to increased recognition of MAFLD in the current era. Long-term studies of incidence and management of late post-transplant cardiovascular morbidity is difficult to assess in single centres due to incomplete data and heterogeneity in the definition of CVD between studies (144).

Post-transplant multi-disciplinary care, and optimisation of cardiovascular risk factors are crucial to prevent late cardiovascular events (7). The utility of predictive cardiovascular risk scores has previously been studied in LT recipients, with the Prospective Cardiovascular Munster Study (PROCAM) score found to have a C statistic of 0.778 in discriminating LT recipients at-risk of future events (250). Since this 2006 study, more predictive scores have been created for pre-transplant and post-transplant patients, however, none have been tested prospectively in large studies (198). VanWagner et al. created a risk calculator for predicting post-transplant cardiovascular risk, factoring in age, demographics, cardiovascular risk factors and diagnoses with a C statistic value of 0.77 (adjusted) (251). The CAR-OLT risk calculator is universally accessible (www.carolt.us) and is used to predict the risk of all CVDs, rather than CAD alone.

Patients with CAD pre-transplant have previously been shown to be at increased risk of cardiovascular mortality post-transplant (252), and as such increased vigilance in these patients is

necessary. A recent systematic review and meta-analysis found that the mortality rate in patients with pre-transplant CAD was 8.1%, and that cardiac-related mortality made up 0.8% of causes of death (150). These findings demonstrated that pre-transplant CAD was a risk factor for both overall (OR 1.4, 95% CI 1.4-1.4, p = 0.01) and cardiac related mortality (OR 1.2, 95% CI 1.1-1.3, p=0.03) (150). CAD with appropriate revascularisation was shown to have similar outcomes to those LT candidates without CAD, and hence CAD should not be a contraindication to LT (152, 248). The largest single centre study of cardiovascular mortality comes from the US, showing a late cardiovascular mortality rate of 10.7% among 775 LT recipients. Predictors of cardiovascular events included age, diabetes, hypertension and male gender (163).

Australian data revealed that despite an overall reduction in the incidence of post-transplant cardiovascular mortality in 30 years, cardiovascular deaths were still responsible for 15% of all late post-transplant mortality. This incidence rate remains substantially higher than the cardiovascular mortality rate in the general Australian population (2). Sudden cardiac death at any point post-transplantation was also investigated in the Australian LT population by Koshy et al. using the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) network. Overall, sudden cardiac death was the most common mode of cardiovascular death post-transplant (32%), particularly in patients with pre-transplant diabetes (aHR 2.5 95% CI 1.25-7.8, p = 0.01) (166). This increased risk of sudden cardiac death is attributed to the escalating rates of metabolic syndrome and CVD post-transplantation (166), further emphasising the need to mitigate cardiovascular risk factors.

In the long-term, post-transplant heart failure continues to be a predominant issue. In a recent study of the incidence of hospitalisations for CVD in LT recipients over a 10-year period, there was a statistically significant increase in presentations with CVD (253). The largest increase was seen for

admissions with heart failure or arrhythmia problems in the setting of LT, estimated at 20% in 2011, a significant increase since 2002 ($p < 0.03$) (253). This change has also been demonstrated in more recent studies; the reported incidence of new post-transplant heart failure being 10% in some studies. Identified risk factors for post-transplant heart failure include systemic HT, DM, and obesity (80, 120).

1.11.6 Rejection and cardiac dysfunction

Mittal et al. published outcomes of 970 LT recipients and the association between DD and rejection based on the original CCM criteria (40). Notably, significant association was found with grade 2 and 3 DD, pulmonary hypertension, LVEF <50%, and the development of acute cellular rejection (40). It is not clear whether this finding was confounded by other complications of DD, such as AKI, necessitating a switch in immunosuppression, or complex intra-operative issues that may have caused systemic hypoperfusion in the context of CCM. An association has previously been found between DD and graft failure by Josefsson et al. however, in this case series DD was defined solely by E/A ratio and did not exclude patients with pre-existing CVD (93). In 2022, Vetrugno et al. found that grade 2 DD (diagnosed according to the 2016 American Society of Echocardiography) had a significant correlation with early allograft dysfunction ($p < 0.003$), in addition to a trend towards worse 90-day survival post-transplant (254). This was further supported by the findings of Singh et al., using the revised CCM criteria, who found that advanced DD was correlated with early allograft dysfunction in their cohort (79, 254).

With the regard to the type of immunosuppression and cardiac complications, retrospective studies have found no association between post-transplant heart failure and sirolimus use despite its deleterious effect on metabolic syndrome (255). Another randomised control study demonstrated that

everolimus and tacrolimus co-therapy were associated with reduced myocardial fibrosis post-heart transplant. However, no similar study has been conducted in the LT population as yet (256). Though there are recommendations towards minimisation of CNI and a switch to MTORi therapies based primarily on studies in kidney transplant recipients (144, 257), further studies are needed on the safety and efficacy of MTORi in LT candidates. Controversially, MTORi are known to carry a high correlation with development of proteinuria, dyslipidaemia and DM, which are all CVD risk factors in themselves. More information is needed before making safe recommendations on dosing and type of immunosuppression in the presence of cardiac dysfunction in LT candidates.

1.12 Management of heart failure post-transplant

The management of heart failure post-transplant is based on the principles of managing heart failure in the general population. Specific management recommendations for LT recipients is lacking and are based primarily on expert advice. Firstly, given those patients with myocardial changes are at risk of clinical heart failure, echocardiographic surveillance every 6 months until 2 years post- transplant was recommended by the Advancing Liver Therapeutic Approaches taskforce implemented in North America (33). With the development of hypertension in at-risk patients post-LT, the first line use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers is advised given their benefit in cardiac remodelling (5). Furthermore, post-transplant DM, whether new onset or longstanding, benefits from the use of sodium-glucose co-transporter 2 (SGLT2) inhibitors such as empagliflozin. Not only do these agents have a potent effect on glycaemic control, but they have renal and cardiac protective effects. In patients with heart failure, with or without preserved ejection fraction, SGLT2 inhibitors reduce cardiovascular related morbidity and mortality regardless of the presence of DM (258, 259). As previously mentioned, the safety and efficacy of these agents have not been studied in the liver transplant population, but they represent a good therapeutic option for

patients with diabetes and CVD in the absence of contraindications such as recurrent urinary tract infection and hypoglycaemia (260).

1.13 Conclusion

The interplay between the heart and liver highlights the multi-system consequences of decompensated cirrhosis. Other than single-centre studies, there are significant gaps in the LT literature owing to the historically low rate of CVD in patients who are not only referred but accepted for LT. However, CVD is likely to become an increasingly common issue with older, more comorbid LT candidates. It is hypothesized that pre-existing cardiac dysfunction, and CAD do increase the peri-operative risk and post-transplant morbidity in liver transplant candidates. There is a need for a nationally standardised risk factor based investigation of myocardial dysfunction and CAD. Subsequent timely treatment of these conditions has the potential to impact LT suitability and long term post-transplant survival.

Chapter 2

Study of Cardiac Dysfunction in LT candidates in South Australia

This paper was published in Clinical Transplantation in April 2022. The listed authors and their contribution are as follows:

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2.1 Abstract

The prognostic role of cardiac dysfunction in cirrhotic patients is increasingly recognised. We studied its impact on morbidity and mortality before and after liver transplantation (LT) including development of post-transplant cardiovascular disease (CVD). In this retrospective study, cirrhotic patients who underwent LT assessment from January 2010 to December 2020 were reviewed. Demographics, cardiac investigations and clinical course were analysed to identify prevalence of cardiac dysfunction and its impact in LT outcomes. Survival analysis was performed using Cox proportional hazard regression modelling, with LT as a time-varying covariate and as an interaction variable with cardiac dysfunction. 308 patients (70% male) were studied. The median (interquartile range) age at LT assessment was 56 (12) years. Cardiac dysfunction was found in 178 (58%) patients

(diastolic, 169; systolic, 26; both, 17) and was significantly associated with hepatorenal syndrome/acute kidney injury and peri- and post-transplant morbidity (adjusted odds ratio [aOR] 1.94, 95%CI 1.06–3.52, $p < 0.001$; aOR 2.01, 95%CI 1.06–3.82, $p = 0.033$; aOR 1.9, 95%CI 1.01–3.65, $p = 0.023$, respectively). Cardiac dysfunction was not associated with mortality before (adjusted hazard ratio [aHR] 1.01, 95% CI 0.99-1.01) or after LT (aHR 0.74, 95% CI 0.4-1.05. Post-transplant CVD (61% cardiac failure) occurred in 36 patients and had no significant association with cardiac dysfunction ($p = 0.11$). Cardiac dysfunction was common in LT candidates and was significantly associated with morbidity before and after LT. Studies on the role of advanced echocardiographic parameters to improve diagnosis of cardiac dysfunction and optimise LT outcomes are needed.

2.2 Introduction

Cardiac dysfunction in LT candidates is increasingly recognised as a leading cause of morbidity and mortality before and after transplantation (1, 2). CCM is reported to occur in 30–80% of patients with advanced cirrhosis (16). In addition to CCM, CAD and porto-pulmonary hypertension (PPHTN) are important causes of cardiac morbidity in LT candidates (4, 5). The role of cardiac assessment in LT candidates has become increasingly important with a change in the demography of LT candidates (27), as elderly and patients with comorbidities, such as DM and CVD, are increasingly considered for LT (6, 7). CCM is usually latent, however, clinical presentations with heart failure and arrhythmias are reported in the early post-transplant period due to the underlying cardiac dysfunction (119). CCM is defined as the presence of SD and/or DD in cirrhotic patients in the absence of other causes of cardiac dysfunction. The 2005 World Congress of Gastroenterology criteria for diagnosis of CCM defined SD as LVEF <55% or blunted increase in CO under stress; DD is defined primarily by E/A ratio, <1 (45).

The measurement of left ventricular function can be complicated in the setting of hyperdynamic circulation secondary to cirrhosis and portal hypertension. The original diagnostic criteria for CCM relies on load-dependent measurements which can be inaccurate in this population. In line with advances in cardiac imaging, sensitive echocardiographic measures, such as Global longitudinal strain (GLS) measurement using speckle tracking have been increasingly investigated in CCM (261). The recently established CCM Consortium has proposed a move away from flow- and load-dependent criteria for CCM in 2019 (5). These criteria suggest measuring SD using advanced echocardiographic parameters such as GLS in patients with normal EF and measuring advanced DD using multiple tissue Doppler parameters (5). Recently, several studies have also suggested a higher cut-off for LVEF, with one study finding the LVEF of 60% as the inflection point for correlation with worse short- and long-term mortality in patients with MELD score >20 (262). The impact of cardiac dysfunction on morbidity and mortality after LT is also controversial (40, 122, 123). Many studies attempted to identify predictive factors of adverse cardiovascular outcomes post-transplant, given the prominence of post-transplant CVD and CVD related mortality in LT recipients. This helps to establish the case for cardiac assessment using the new improved criteria in routine clinical practice. Australian literature on cardiac dysfunction in LT candidates is limited to studies investigating CAD workup and post-transplant cardiovascular mortality (2, 88, 166). Hence, the primary aim of this study was to assess the prevalence of cardiac dysfunction in cirrhotic patients undergoing LT evaluation in a state-wide LT unit and to study its impact on morbidity and mortality before and after LT including post-transplant CVD.

2.3 Methods

2.3.1 Study population

This was a retrospective, observational cohort study of patients who underwent LT assessment at the SALTU from January 2010 to December 2020. Patients with non-cirrhotic indications for LT including patients with acute liver failure, metabolic or genetic disorders, hepatocellular cancer without cirrhosis, those with insufficient transthoracic echocardiography details and those assessed for re-transplantation were excluded. The examined cohort was followed until the end of February 2021, death or loss to follow-up. Demographic data were collected from electronic medical records, comprising age, gender, MELD score, cardiovascular comorbidities and aetiology of liver disease. Cardiovascular comorbidities included hypertension, DM, pre-existing CVD covering moderate to severe valvular pathologies, pre-existing CAD and pulmonary hypertension.

2.3.2 Cardiac investigations

All available cardiac investigations (transthoracic and dobutamine stress echocardiogram, angiogram and electrocardiogram) and prior cardiac diagnoses were reviewed. Cardiac dysfunction was defined as the presence of SD and/or DD. SD was defined as LVEF <55%, or blunted increase in CO under stress as per the 2005 World Congress of Gastroenterology criteria for diagnosis of CCM (54). DD is defined primarily by E/A ratio, <1. However, this is a preload-dependent measurement, and could be fallacious in patients with decompensated cirrhosis with frequent fluid shifts. Rather than defining DD by E/A ratio alone, we defined DD incorporating 2016 ASE Guidelines as follows (94):

1. presence of three or more of the following echocardiographic parameters:
    a) average transmitral Doppler early filling velocity/tissue Doppler early diastolic mitral annular velocity (E/e') ratio >14,
    b) septal e' velocity ≤7 cm/s,

c) tricuspid regurgitation velocity >2.8 m/s,

d) LAVI >34 ml/m^2; or

2. abnormality in two of the above parameters with abnormal E/A ratio; or
3. when echocardiogram was reported as having DD.

The grade of DD was taken as reported in the echocardiogram report. Severe cardiac dysfunction was defined as SD and/or the presence of grade 3 DD.

2.3.3 Definition of clinical outcomes

We defined pre-transplant morbidity by three or more unplanned hospital admissions for the purpose of this study. Additionally, specific data were collected on refractory ascites (RA), AKI and HRS, as these clinical events are a major source of morbidity and hospitalisation in decompensated cirrhosis. RA was defined ascites that was intolerant or intractable to diuretics requiring repeated paracentesis. AKI was defined in accordance with European Association for the Study of the Liver guidelines as an increase in serum creatinine ≥26.5 μmol/L within 48 hours or a percentage increase in serum creatinine ≥50% in 7 days (128). Because it was a retrospective study, the diagnosis of HRS was as established by the treating hepatologist in accordance with European Association for the Study of the Liver guidelines.

Peri-operative morbidity was defined as transplant admission ≥14 days, or any of the following complications; peri-operative hypotension; AKI; heart failure; need for cardiology specialist input, surgical complications, rejection or infection requiring systemic antibiotics.

Post-operative morbidity was defined by the development of heart failure, CAD, severe arrhythmia, CKD, stroke, rejection or severe systemic infection requiring hospitalisation after discharge from LT admission.

Post-transplant CVD included development of any of the complications after admission for LT including CAD, heart failure, arrhythmia and/or stroke. Heart failure was clinically diagnosed by the treating physician with treatment using diuretic therapy. Post-transplant echocardiograms were not routinely accessible.

2.3.4 Statistical analysis

Descriptive statistics were performed using median (IQR) for continuous variables and frequency (percentage) for categorical variables. Univariate analysis to compare characteristics of patients with and without cardiac dysfunction, pre-, peri- and post-transplant morbidity, and post-transplant CVD was performed using Chi-squared tests of independence for categorical variables and independent *t*-tests or Mann–Whitney tests for continuous variables as appropriate. Variables significant at $p = 0.10$ in univariate analysis, or with a pre-established clinical significance were included in multivariate analysis which was performed using binary logistic regression. Results were presented as adjusted odds ratio (aOR), 95% confidence interval (95% CI) and *p*-values (provided to three decimal places).

Estimated overall survival was assessed using the Kaplan-Meier curves. Cox proportional hazards regression modelling with time-varying covariates was performed to establish associations between LT and cardiac dysfunction on survival with age and gender included as covariates. Fixed effects included LT as a time-varying covariate, cardiac dysfunction and an interaction with cardiac dysfunction. Results were presented as aHR, 95%CI and two-tailed p-values (provided to three

decimal places); p-value < 0.05 was considered statistically significant. IBM SPSS Statistics for Windows, Version 27.0, and STATA for Windows version 16 were used for analysis. This study was approved by the Southern Adelaide Human Research Ethics Committee reference number: LNR/21/SAC/19.

2.4 Results

2.4.1 Patient demographics

A total of 366 patients underwent LT assessment during the study period; 58 patients were excluded due to non-cirrhotic indications for LT, such as acute liver failure, metabolic liver diseases and hepatocellular carcinoma (*n* = 39), limited echocardiographic data (*n* = 18) and re-transplant (*n* = 1), leaving a study cohort of 308 patients (Table 2.1). These patients were followed for a median (IQR) of 1043 (1945) days. Baseline demographic data are presented in Table 2.1. As expected, the majority of LT candidates were Caucasian (254, 82%), followed by Asian or other heritage (43, 14%), and eight persons of Aboriginal or Torres Strait Islander heritage, of whom five were successfully transplanted. CVD prior to LT was present in 33 (11%) patients (CAD, *n* = 21, valvular heart disease, *n* = 12 and resolved peripartum cardiomyopathy, *n* = 1). One patient had a combination of CAD and valvular heart disease. Thirty-two patients underwent CA prior to LT, and seven patients had significant lesions detected; of these seven, three underwent percutaneous coronary intervention, one patient underwent coronary artery bypass grafting and three patients were managed conservatively. Data on CAD pre-transplant is described in more detail in chapter 3.

Table 2.1: Patient demographic data

(n=308)	
Age (median, IQR) years	56 (12)
Male, *n* (%)	215 (70)
MELD, median (IQR)	16 (7)
Na-MELD, median (IQR)	18 (10)
Hypertension, *n* (%)	66 (21)
DM, *n* (%)	91 (30)
Pre-existing CVD, *n* (%)	33 (11)
HRS/AKI, *n* (%)	101 (33)
Cardiac dysfunction, *n* (%)	178 (58)
Aetiologies of cirrhosis, *n* (%)	
MAFLD	67 (22)
Alcohol	99 (32)
Hepatitis B/C	73 (23)
Autoimmune	40 (13)
Other	29 (9)
Ethnicity, *n* (%)	
Caucasian	(254, 82)
Asian	14 (5)
Other	29 (9)
Indigenous Australian	8 (3)

2.3.2 Prevalence of cardiac dysfunction and its predictors

Based on echocardiographic findings, cardiac dysfunction was evident in 178 (58%) patients. A diagnosis of pre-existing cardiac disease was present in only 20 of these patients, attributing the majority (*n* = 158, 89%) of the observed cardiac dysfunction to CCM. QT prolongation was also highly prevalent (*n* = 188, 61%). In our cohort, QT prolongation was associated with CD both on univariate analysis (p = 0.007), and multivariate analysis (aOR 2.11, 95% CI 1.06-4.20, p = 0.033). DD was seen in the majority (mild to moderate *n* = 166; severe *n* = 3). The individual parameters of DD in median (IQR) were as follows: E/e' ratio 9.5 (4), LAVI 27 (14) ml/m^2, septal e' 8 (2.5) cm/s, maximal tricuspid regurgitation 2.5 (0.6) m/s and E/A ratio 1.1 (0.6). SD was evident in 26 patients; 10 of these patients had abnormal myocardial function on dobutamine stress echocardiogram with EF >55% at rest. Seventeen patients had both SD and DD. Predictors for the presence of cardiac dysfunction on univariate analysis were advanced age, DM and MAFLD (Table 2.2). On multivariate analysis only age and DM were independently associated with cardiac dysfunction.

Table 2.2: Predictors of cardiac dysfunction in LT candidates

			Univariate analysis	Multivariate analysis		
	With CD *n* = 178	Without CD *n* = 130	*p*-value	aOR	95%CI	*p*-value
Age (median, IQR) years	59 (10)	53 (15)	<0.001	1.07	1.04–1.1	<0.001
Male, *n* (%)	128 (72)	87 (67)	0.38	0.95	055–1.64	0.864
MELD, median (IQR)	16 (7)	16 (7)	0.93	0.95	0.85–1.06	0.330
Na-MELD, median (IQR)	19 (9)	17 (11)	0.598	1.05	0.95–1.16	0.380
Hypertension, *n* (%)	45 (25)	21 (16)	0.067	0.85	0.43–1.66	0.620
DM, *n* (%)	67 (38)	24 (18)	<0.001	2.00	1.09–3.64	0.024
Pre-existing CVD, *n* (%)	25 (14)	8 (6)	0.009	0.62	0.29–1.33	0.220
HRS/AKI, *n* (%)	66 (37)	35 (27)	0.002	1.76	0.97–3.19	0.063
MAFLD, *n* (%)	46 (26)	19 (15)	0.025	0.85	0.42–1.74	0.663

2.4.3 Clinical outcomes

2.4.3.1 Pre-transplant morbidity and mortality

Pre-transplant morbidity was observed in 181 (59%) LT candidates. HRS/AKI occurred in 101 (33%) patients and was the only independent predictor of pre-transplant morbidity (aOR 5.279, 95% CI 2.74–10.15, $p < 0.001$). Univariate and multivariate analyses identified cardiac dysfunction, age, high MELD score and MAFLD as significant independent predictors of HRS/AKI pre-transplant (Table 3). One patient with an LVEF of 34% was treated with cardiac resynchronisation therapy to achieve normalisation of systolic function and is awaiting LT at the time of writing.

2.4.3.2 Mortality outcomes in patients with severe cardiac dysfunction

During the study period, five patients with SD died before transplant. Four of these deaths were due to progression of liver disease; one patient with LVEF 29% and grade 3 DD developed severe cardiogenic shock and multiorgan dysfunction. This is the only LT candidate who was precluded from LT due to cardiac dysfunction. Among the two other patients with grade 3 DD, one died pre-transplant and the other had a successful transplant.

2.4.4 Liver transplantation

One hundred and ninety-seven (64%) patients underwent LT successfully and 83 (27%) patients died waiting for LT. Twenty-eight (9%) patients remained alive at the end of the study without LT, of which 19 were on transplant waitlist, while nine were excluded from LT due to improved MELD scores, comorbidities or progression of hepatocellular cancer.

2.4.5 Peri-operative morbidity

Peri-operative morbidity (including cardiac failure, AKI, rejection, infections and surgical complications) was seen in 127 (64%) patients, with many patients experiencing multiple complications. The median (IQR) hospital stay was 19.5 (16) days in those with peri-operative morbidity compared to 14 (6) days in those without complications. Pre-transplant cardiac dysfunction was evident in 80 (41%) of patients with peri-operative morbidity. This was the only predictor of peri-operative morbidity (Table 2.3) on univariate and multivariate analyses. New onset heart failure was the single most common peri-operative event (n = 21). Prior asymptomatic cardiac dysfunction was present in 13 of these patients (grade 1 and 2 DD in 11 patients: SD in 2 patients). Heart failure persisted or worsened after discharge from LT admission in five patients. There were no episodes of

CAD. One patient who experienced severe bleeding and cardiac arrest during the reperfusion phase died 4 days later. He did not have any pre-transplant cardiac dysfunction.

Table 2.3: Predictors of HRS/AKI, peri operative and post-operative morbidity in LT candidates

	Univariate analysis	Multivariate analysis		
	p-value	aOR	95%CI	*p*-value
HRS/AKI pre-transplant (*n* = 204)				
Age	0.025	1.02	0.99–1.06	0.150
MELD	0.002	1.14	1.09–1.19	<0.001
Male gender	0.792	0.81	0.44–1.48	0.809
CD	0.002	1.94	1.06–3.52	0.029
MAFLD	<0.001	3.47	1.73–6.98	<0.001
DM	0.063	0.92	0.47–1.78	0.796
Peri-operative morbidity (*n* = 127) *				
Age	0.673	0.99	0.96–1.03	0.732
Male gender	0.521	0.79	0.40–1.54	0.487
Cardiac dysfunction	0.023	2.01	1.06–3.82	0.033
DM	0.250	1.46	0.72–2.95	0.298
MELD	0.331	1.03	0.98–1.08	0.303
Post-operative morbidity (*n* = 83) **				
Age	0.005	1.01	0.98–1.05	0.404
Male gender	0.046	0.14	0.31–1.19	0.124
Cardiac dysfunction	0.003	1.90	1.01–3.65	0.023
HRS/AKI	0.016	1.82	0.88–3.74	0.104
Peri-operative morbidity	0.010	2.04	1.06–3.91	0.033
Pre-LT CVD	0.018	3.78	1.17–12.25	0.027

*Peri-operative morbidity defined as transplant admission ≥14 days, or any of the following complications: peri-operative hypotension, AKI, heart failure, need for cardiology specialist input, surgical complications, rejection, or infection requiring systemic antibiotics.

**Post-operative morbidity defined as the development of heart failure, CAD, severe arrhythmia, CKD, stroke, rejection or severe sepsis (systemic infection requiring hospitalisation).

2.4.6 Post-operative morbidity

Post-transplant morbidity (including post-transplant CVD, CKD, rejection and severe sepsis) was observed in 83 (41%) patients, within the median (IQR) post-transplant follow-up time of 4.3 (5.5) years. Pre-transplant cardiac dysfunction was evident in 58 (72%) patients with post-transplant morbidity. Univariate analysis revealed age, male gender, pre-transplant cardiac dysfunction, pre-transplant CVD and peri-operative morbidity to be associated with post-transplant morbidity (Table 2.3). Multivariate analysis confirmed independent predictors to be pre-transplant cardiac dysfunction, peri-operative morbidity and pre-transplant CVD.

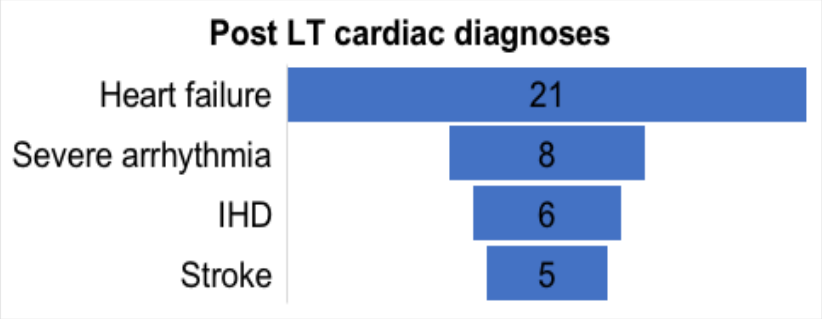

Figure 2.1: Post-transplant cardiac diagnoses

2.4.7 New onset post-transplant CVD

Post-transplant CVD was seen in 36 patients, and 27 of these patients had no prior history of CVD. The median (IQR) time to a cardiac event after LT was 458 (1234) days, with nine events occurring in the first 100 days after discharge (7 heart failure, 1 CAD and one stroke). New onset heart failure post-transplant was the most common diagnosis (n = 22), followed by severe arrhythmia (n = 8),

CAD (*n* = 6) and stroke (*n* = 5) (Figure 2.1). Five patients experienced multiple new cardiovascular events after transplant. Of the 22 patients with post-transplant heart failure, 15 (68%) had pre-transplant cardiac dysfunction; five had both SD and DD, and the remainder had only DD. When these patients were reviewed for the presence of pre-existing CVD, it was evident that three patients had CAD and two had valvular heart diseases (one patient had incidental moderate aortic stenosis and the other patient was treated with tissue aortic valve replacement pre-transplant). There was no clinical evidence of heart failure prior to LT in these patients.

2.4.7.1 Predictors of post-transplant CVD

Pre-transplant cardiac dysfunction was present in 25 (69%) of patients who developed post-transplant CVD, however, no statistical significance was seen (p = 0.11). Nevertheless, presence of pre-transplant CVD was an independent predictor of post-transplant CVD (aOR 5.07, 95%CI 1.76–14.61, p < 0.003).

2.4.8 Incidence and outcomes of porto-pulmonary hypertension in LT candidates

Screening and detection of PPHTN is a routine part of the cardiac workup in LT candidates. In our cohort 68 (22%) echocardiograms could not provide an estimation of pulmonary artery pressure (ePAP). Some echocardiograms also failed to report on other parameters of the right heart to guide suspicion of right heart dysfunction or pulmonary vascular pathology. In total, 17 right heart catheters (RHC) were performed in our cohort. Thirteen of them were negative for significant PPHTN. Of these 13 normal RHC studies, five patients had a final diagnosis of hepatopulmonary syndrome (HPS). The results of the four patients with abnormal RHC are summarised in Table 2.4. Only one patient with pre-transplant PPHTN successfully proceeded to LT. Despite sildenafil therapy, severely

elevated pulmonary artery pressures were detected during the LT operation, requiring intravenous epoprostanol infusion post-operatively.

Table 2.4 Summary of cardiac investigations for patients with post-transplant pulmonary hypertension

Patient number	**Gender**	**RHC result**	**TTE finding**	**Clinical outcome**
1	Male	mPAP 36mmHg	Grade 2 DD	HCC progression, death
2	Male	mPAP 55mmHg	Grade 1 DD	Death
3	Female	mPAP 34mmHg	Normal TTE	Successful LT
4	Male	mPAP 32mmHg	Grade 1 DD	Successful LT

There were four patients who received LT where echocardiograms failed to detect evidence of PPHTN:

The first patient was found to have reduced right ventricular function in the intensive care unit immediately post-transplant with ePAP of 82mmHg. Pre-transplant TTE showed evidence of grade 2 DD with no history of CAD. There was successful response to macitentan and sildenafil.

The second patient had a known history of CAD pre-transplant, but otherwise normal echocardiogram during LT workup. Mild right ventricular dysfunction was detected in the intensive care unit, with improvement after commencing vasodilator therapy to 34mmHg on formal RHC and eventual weaning of therapy.

The third patient had no pre-existing heart disease, and grade 1 DD found during transplant workup. The intra-operative pulmonary pressures were 50mmHg, requiring commencement of vasodilator therapy with gradual response over 2 years.

The fourth patient had a normal echocardiogram including no evidence of right ventricular failure during LT workup. However, cardiopulmonary exercise testing (CPET) showed the abnormal oxygen uptake/work rate relationship and low oxygen pulse suggesting an oxygen delivery limitation. The raised VE/VCO^2 slope was consistent with significant pulmonary vascular abnormality. The patient proceeded to LT where mean PAP of 108mmHg was found on induction of anaesthesia and insertion of Swan-Ganz catheter. The LT procedure was abandoned, and the patient underwent 3 months of vasodilator therapy to achieve mean PAP of 30mmHg on repeat RHC. The patient again proceeded to LT and intra-operatively developed cardiac arrest in the setting of post-reperfusion syndrome and variceal bleeding, with subsequent multiorgan failure and death 4 days later.

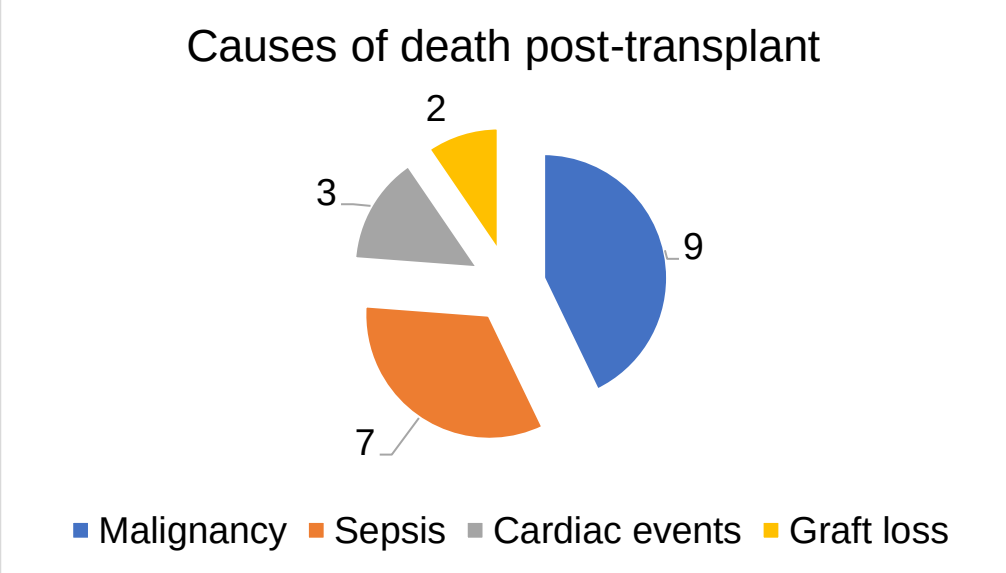

Figure 2.2: Causes of death post-transplant

2.4.9 Survival outcomes

Of the 104 deaths that occurred during the study period, 83 occurred pre-transplant and 21 post-transplant. Causes of post-transplant death included malignancy (*n* = 9), severe sepsis (*n* = 7), CVD (*n* = 3) and graft loss (*n* = 2) (Figure 2.2). There were three instances of cardiovascular mortality, of which two were not associated with pre-transplant CVD or cardiac dysfunction: one death occurred

due to cardiogenic shock during LT surgery and the other from cardiorenal syndrome at 9 months. It is possible that their cardiac dysfunction was not diagnosed by the echocardiographic criteria in use at the time. The third death was fatal CAD that occurred 3.5 years post-transplant (with a known history of CAD and grade 2 DD pre-transplant). As expected, LT was associated with improvement in survival (aHR 0.072, 95%CI 0.033–0.1, $p < 0.001$). There was no association between cardiac dysfunction and survival either pre-transplant (aHR 1.01, 95%CI 0.99–1.01, $p = 0.32$) or post-transplant (aHR 0.74, 95%CI 0.4–1.05, $p = 0.112$) after adjustment for age and gender (Figure 2.3 and 2.4). QT prolongation also failed to show association with post-transplant morbidity or mortality.

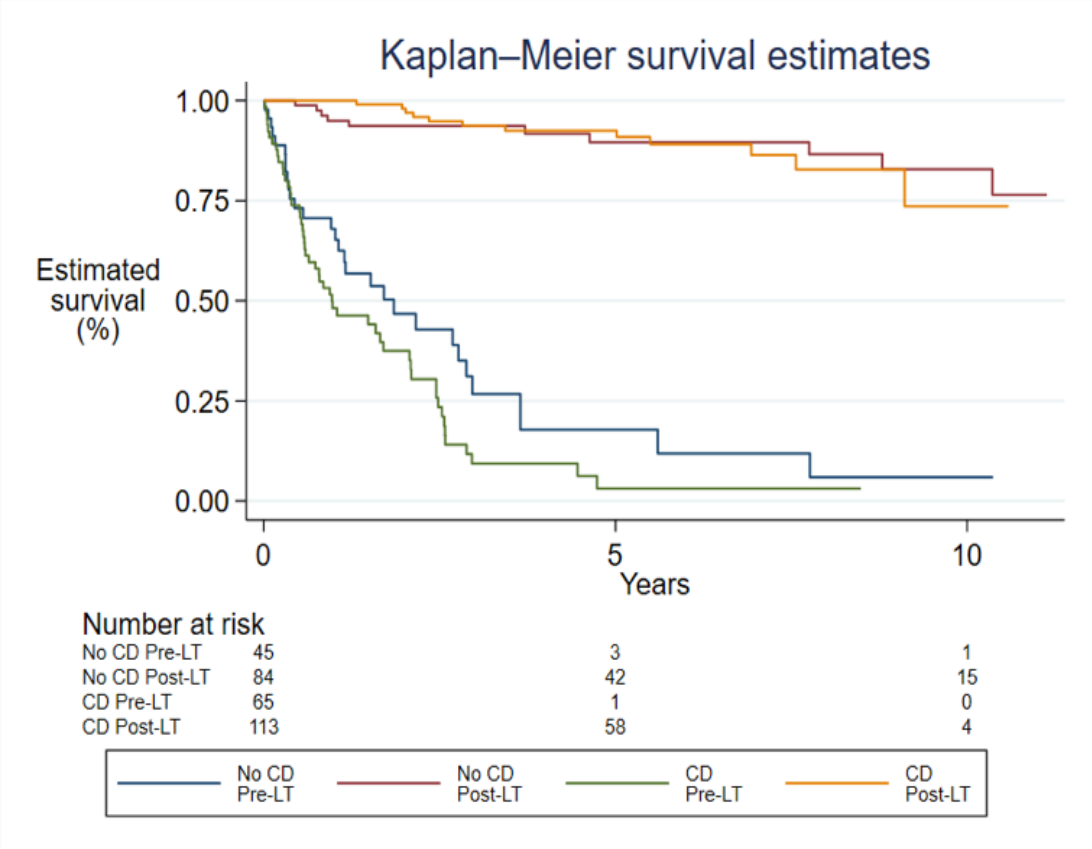

Figure 2.3. Kaplan-Meier survival estimates for LT candidates with or without CD, pre- and post-transplant.

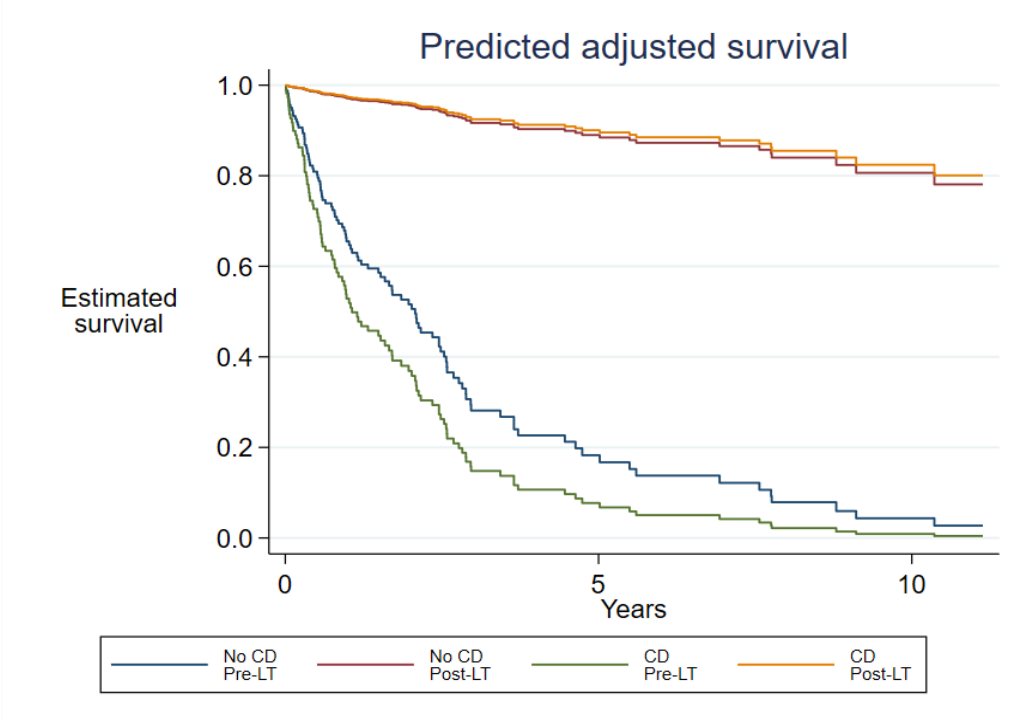

Figure 2.4:Estimated survival from mortality in LT candidates with or without CD. Predictions obtained using Cox regression with adjustment for age and gender.

2.5 Discussion

Cardiac dysfunction in LT candidates including CCM has garnered significant interest recently due to association with pre-transplant HRS and post-transplant cardiovascular morbidity and mortality (80, 263). In this study the impact of cardiac dysfunction due to all causes, including pre-existing cardiac disease and CCM on transplant outcomes, was explored. We found that cardiac dysfunction was frequently observed in LT candidates and was associated with HRS/AKI before LT. Although cardiac dysfunction detected before LT was significantly associated with peri- and post-operative morbidity, it was reassuring that it did not predispose to any increased mortality before and after LT.

In our cohort of 308 LT candidates, mild to moderate cardiac dysfunction was widely prevalent at 58% and most manifested as DD similar to other reports in the literature (80). The reported prevalence

of cardiac dysfunction in patients with liver cirrhosis varies from 15% to 80% depending on the diagnostic criteria applied (16, 40, 122). Mittal et al. defined DD using only E/A and E/e' ratios and reported a prevalence of 15% (40). Another study that evaluated a relatively small cohort of patients with cirrhosis defined DD based on combination of septal e' 8 cm/s and lateral e' 10 cm/s and reported a prevalence of 38% (39). Using the updated criteria for CCM, Izzy et al. reported a prevalence of 35% in LT candidates (80). Sonny et al. reported a prevalence of 54% DD in a retrospective study of patients who underwent LT using multiple echocardiographic parameters as in our study (122). As our cohort consisted of patients who underwent LT assessment, it is not surprising that severe cardiac dysfunction was uncommon. Advanced (grade 3) DD was much higher in the study by Mittal et al. (40), which was not the case in other studies that evaluated LT candidates (80, 122). The low frequency of SD seen in our study is supported by other studies (80). Independent predictors of cardiac dysfunction in our cohort included DM and advanced age, similar to other studies (80, 122). Cardiac dysfunction was also more frequent in those with MAFLD cirrhosis. MAFLD is increasingly recognised to cause myocardial remodelling (8, 33), in addition to being an independent risk factor for fatal and non-fatal CVD (22, 25, 264, 265).

Cardiac dysfunction was associated with HRS/AKI, validating the findings of prior studies that DD is a significant contributor in developing HRS (72, 263). HRS/AKI was a cause of morbidity in one-third of our cohort and was associated with cardiac dysfunction, MAFLD, increasing age and MELD. The traditional pathophysiological model for HRS includes excessive arteriolar splanchnic vasodilation (45) causing hypoperfusion to the kidneys, in addition to chronic systemic inflammation causing glomerular sclerosis and cell death (16, 62). In addition, there is increasing recognition that impaired myocardial reserve is a major contributor to the development of HRS, particularly when the newly revised diagnostic criteria of CCM is used (79). While LT is the optimal treatment for both

HRS and CCM, the ensuing multi-organ dysfunction compounds the hemodynamic shifts during LT, increasing the risk of cardiovascular mortality by up to 40% during the peri-operative and early post-transplant period (73, 89).

Over 50% of our LT patients experienced peri-operative and/or post-operative morbidity. Cardiac dysfunction was a significant predictor of peri-operative and post-transplant morbidity. Heart failure was the single most common peri-operative event in these patients. This is consistent with a recent study that highlighted arrythmias and heart failure to be leading causes of early morbidity post-transplant (266). Occurrence of peri-transplant heart failure highly correlated with peri-transplant morbidity and mortality in a single-centre European study (109). Forty percent of our patients with heart failure in the peri-transplant period had no evidence of cardiac dysfunction before LT. In addition, two patients who died post-transplant with cardiac arrest and failure, respectively, had normal cardiac evaluation pre-transplant. This raises the possibility of subclinical CCM becoming clinically overt due to the hemodynamic stress of LT surgery. If more sensitive criteria such as GLS or global myocardial work index were used, the frequency of cardiac dysfunction would have been higher. Hence, our findings reiterate the importance of more sensitive measures of cardiac function before transplant. DD identified before LT was a significant predictor of liver allograft rejection, graft failure and death in a retrospective study spanning over a decade (40). Interestingly, the frequency of these adverse outcomes was in accordance with the severity of DD with grade 3 dysfunction associated with increased mortality and frequent LT rejection.

Prevalence of post-transplant CVD (18%) in our study was similar to the literature (80)·(22). Cardiac dysfunction detected before LT had no statistically significant association with post-transplant CVD, although 69% of these patients had cardiac dysfunction before LT. This lack of significance may be

due to the smaller number of events. This is discordant with other studies that showed that cardiac dysfunction predicted post-transplant CVD (80, 120, 122). In addition to DD, Qureshi et al. also found pre-transplant hemodynamic parameters, such as mean arterial pressure, mean pulmonary artery pressure and mean pulmonary capillary wedge pressures, to be associated with post-transplant new onset heart failure (120). CCM defined by the new criteria was found to be associated with increased risk of post-transplant CVD (80). In addition to the composite diagnosis of CCM, individual echocardiographic parameters of DD (such as E/e', septal e' velocity and LAVI) and systolic function (such as GLS) were found to be predictive of post-transplant heart failure (80, 122). Among the post-transplant CVD, heart failure was the most common cardiovascular diagnosis after LT in our cohort. Review of echocardiographic findings for worsening disease was not carried out at the time of events. While early studies showed promise that CCM changes reversed post-transplant (5, 42), a study of cardiac MRI on cirrhotic patients showed occurrence of significant myocardial fibrosis proportionate to the duration and severity of cirrhosis (112). This may persist and contribute to post-transplant CVD, as demonstrated by Dowsley et al. (92). Post-transplant worsening of DD was reported by Sonny et al. albeit with no clinical correlation (122).

Mortality outcomes of our cohort post-transplant were consistent with previous studies (16, 80), with malignancy and infection being the leading causes. While the incidence of post-transplant cardiovascular mortality has declined, it remains a substantial cause of death (2). Post-transplant cardiovascular death in our cohort was infrequent (n = 3). A review of Australia & New Zealand Liver and Intestinal Transplant Registry revealed that sudden cardiac arrest was the most common cause of cardiovascular mortality, more so in the contemporary era (166). The risk factors were pre-transplant DM, advanced age, CAD and MAFLD aetiology. The study raised awareness about risk stratification and targeted management in high-risk patients.

We found no association between cardiac dysfunction and mortality, similar to other contemporary studies (2, 22, 80, 122). However, most of these single-centre studies, including our own, had small case numbers. Larger cohort studies of LT candidates found advanced DD (grades 2 and 3) to be related to higher all-cause mortality (40). The lack of association between cardiac dysfunction and post-transplant mortality in our study could be due to the relatively infrequent occurrence of severe DD or as previously mentioned, the lack of sensitivity of the criteria used. In those studies where DD was a significant predictor of death, DD was defined by individual parameters, such as deceleration time, E/A ratio <1 and/or E/e' ratio >10 (40, 93, 109). While QT prolongation demonstrated an association with cardiac dysfunction, it did not appear to be a predictor of post-transplant morbidity or mortality in our cohort. Older studies had previously found QT prolongation (a minor measurement of CCM in the original diagnostic criteria) to be a predictor of post-transplant mortality (122). Koshy et al. argued that while QT prolongation is observed more frequently in LT candidates, no association is robustly seen between QT prolongation and the myocardial changes of CCM, despite its association with sudden cardiac death (108). As such, the CCM Consortium have also removed prolonged QT as a supportive criterion for CCM.

Over 20% of screening TTE failed to provide an accurate estimate of PAP due to the hyperdynamic circulation in advanced cirrhosis resulting in a high output cardiac state (267). Reliance on ePAP alone to detect PPTHN is therefore insufficient, particularly given the risk of peri-operative mortality in PPHTN of up to 50% (267). Recent consensus guidelines highlighted that an enlarged or dysfunctional right atrium or ventricle should raise suspicion and investigation of PPHTN (33). The peri-operative risks of PPHTN include the risk of haemodynamic compromise and right ventricular failure (33). As such, the outcomes of LT even in the setting of mild-moderate PPHTN are worse

than in LT recipients without PPHTN (267). Provided there is evidence of an adequate response to vasodilator therapy (mPAP <30-35mmHg), prognosis post-transplant remains promising in carefully selected patients (233). Qureshi et al. also found that PPHTN was a significant predictor of post-transplant heart failure (120). With regard to the death in our cohort that occurred in the setting of likely post-reperfusion syndrome, attributing this death solely to pre-existing CVD is controversial as post-reperfusion syndrome is incompletely understood, and there are complex donor, recipient and procedure related factors that contributed to the immediate post-procedural death (268).

Literature on the use of advanced echocardiography in the diagnosis of CCM and its clinical utility is limited (43). To enhance the diagnostic accuracy of global cardiac function in advanced cirrhosis, in addition to the revised CCM criteria, echocardiographic parameters, such as global myocardial work index (a non-invasive equivalent of myocardial work by invasive pressure volume loop), may be helpful. This is being studied in an ongoing multicentre prospective study (98, 269).

2.6 Limitations and strengths

A strength of this study was the analysis of a well-described, long-term cohort of LT, including analysis of pre- and post-transplant events. All causes of cardiac dysfunction, in addition to CCM were included, and DD defined by multiple parameters. This is more specific than assessing individual parameters, such as E/A or E/e ratio as done in other studies (120, 123). We limited our cohort to cirrhotic patients who underwent LT assessment, and hence the findings cannot be applied to all patients with cirrhosis. Given the retrospective nature of the study, the associations observed cannot be interpreted as being causal. In addition, a detailed review of traditional cardiovascular risk factors including dyslipidaemia and family history of CAD was not possible. Furthermore, the assessment of echocardiogram can be subjective with significant inter-operator variability as well as

variability over time, which was not reviewed. We propose to address these drawbacks with the ongoing prospective study of patients with advanced cirrhosis using advanced echocardiographic measures with follow-up after successful LT to address reversal of CCM (98, 269).

2.7 Conclusion

Mild to moderate cardiac dysfunction, attributed to CCM was widely prevalent in our cohort of LT candidates. It was associated with the development of HRS/AKI before LT, and peri- and post-operative morbidity after LT. Heart failure was the most common cause of cardiac morbidity in the post-transplant period and was not predicted by pre-transplant assessment. We suggest improving the diagnosis of pre-transplant cardiac dysfunction using more sensitive echocardiographic techniques to optimise transplant outcomes.

Chapter 3

Coronary artery disease in LT candidates in SALTU

3.1 Abstract

Liver transplantation (LT) is associated with higher mortality among patients with known CAD undergoing LT. Traditionally, CAD is considered a relative contraindication to LT, however recent studies support appropriate revascularisation carrying similar LT outcomes to patients without CAD. The lack of standardized international guidelines for pre-transplant assessment for screening and follow-up of pre-transplant CAD highlights the need to broaden the diagnostic and management armamentarium of IHD in LT candidates. All LT candidates that were assessed in the South Australian Liver Transplant Unit from 2010 to December 2020 were reviewed retrospectively. Their investigation, management and post-transplant outcomes are presented in this chapter.

Results

Of 366 LT assessments, 22 patients with pre-transplant CAD were identified with median age 62 +/- 8 years. Causes of liver disease in those with pre-transplant CAD included 9 with MAFLD cirrhosis, 8 due to alcohol, and 4 due to viral hepatitis or autoimmune liver disease. One patient was not cirrhotic. Thirteen patients proceeded to LT, 8 patients died without LT and one patient remains on the LT waitlist. Cardiac risk factors including diabetes mellitus (45%), smoking history (59%), hypertension (55%) and obesity (45%) were widely prevalent amongst CAD patients assessed for LT. Anatomic assessment of coronary arteries occurred in 10 patients, with 7 having significant lesions. Computed tomography coronary angiography (CTCA) was only utilised for one patient amongst those with known IHD. Revascularisation occurred in 3 patients. Of the 13 patients that proceeded to transplantation, seven patients experienced CVD, one patient had two new CVD

diagnoses. Post-transplant mortality occurred in 3 patients; two patients had overwhelming sepsis from hepatic abscesses, and there was one sudden cardiac death 3.2 years post-transplantation.

Conclusions

The majority of patients with pre-transplant CAD had MAFLD and alcohol related liver disease. Appropriate revascularisation of significant CAD was undertaken when detected. Amongst the subgroup of patients with pre-transplant CAD, LT was safe with no 30-day mortality events. Despite this, post-transplant CVD was significantly more common in patients with pre-transplant CAD. Coronary angiography either invasive or CT was underutilised. A cardiac risk stratification tool in accordance with recent literature is necessary to optimise cardiac outcomes post-transplant in anticipation of the recent increase in LT candidates at risk of CAD. (88).

3.2 Introduction

Improvements in surgical technique and immunosuppression have dramatically changed LT outcomes over the past three decades. Nevertheless, CAD continues to be a leading cause of post-transplant morbidity and mortality (119). The available literature describes the overall prevalence of ischaemic cardiac events post-transplant to be 1.3–22.7% depending on time elapsed post-transplant (144). Pre-transplant CAD increases both peri-operative and post-operative risk and has been shown to confer a 1 year post-transplant mortality up to 40% (119). An observational study found that CAD contributed to 12% of LT mortality with a functioning allograft (103). The prevalence of CAD in LT candidates correlates closely with the presence of MAFLD and other cardiometabolic risk factors (270). Due to a shift in the LT candidate profile with older patients, more comorbidities, and increasing MAFLD being observed in those referred for LT, pre-transplant CAD is a significant consideration in LT candidates. Treatment of significant CAD pre-transplant either medically or with

revascularisation enables LT candidates to proceed to LT safely (152). Cardiovascular testing is a cornerstone in the workup for adult LT candidates. The current international guidelines regarding cardiac workup pre-transplant from the AHA/ACCF and AASLD advise non-invasive myocardial stress testing based on the presence of 3 or more traditional cardiovascular risk factors (147). Traditionally this is performed using DSE, however, DSE has been shown to lack sensitivity (estimated at 37%) (89) and therefore carries a poor negative predictive value for latent CAD. Prospective studies have demonstrated that negative DSE alone was insufficient to predict the risk of post-transplant CAD events (88). There are new anatomic testing modalities available, such as minimally invasive CTCA. The role of CTCA in the workup of the LT candidate has received increased attention due to its high specificity and sensitivity, comparable to that of invasive CA (89). Accurately detecting those with severe CAD needing revascularisation will limit the need for invasive CA (219). Furthermore, cardiac risk stratification pre-transplant is crucial given the increasing prevalence of metabolic syndrome and accelerated atherosclerosis seen post-transplantation (2, 88).

The aim of this study was to describe the clinical profile of patients with CAD pre-transplant, and their outcomes post-transplant. The secondary aim was to study the onset and outcomes of new onset CAD in LT recipients.

3.3 Methods

Patients who underwent LT assessment in SALTU from 1st January 2010 to 29th February 2020 were reviewed. Patients who had CAD diagnosed prior to LT referral, during LT assessment, or post-transplant were studied in detail. The following details were captured; cardiovascular risk factors, cardiac investigations, pre-transplant morbidity and mortality, peri-operative complications, and

post-operative morbidity and mortality. Cardiovascular risk factor information was collected where available from the electronic medical records.

Any identified coronary lesions were managed according to AHA criteria, whereby revascularisation was undertaken for the following indications: unstable angina, proximal disease, left main equivalent disease, and significant ischaemia on functional testing. Obstructive CAD was defined as a lesion requiring revascularisation, stenosis >70%, or a functionally significant lesion (271). Non obstructive CAD covers 50-70% stenosis without functional significance and all stenosis <50%.

3.3.1 Cardiac investigations

All patients underwent ECG, TTE and further cardiac testing at the discretion of the consulting cardiology team. (94). DSE was defined as positive when there was new or worsening regional left ventricular wall motion abnormality from baseline. Further cardiac investigations including CA and CTCA were also reviewed when available. When coronary atherosclerosis was detected, treatment was planned at the discretion of the consulting cardiology team.

3.3.2 Clinical outcomes

The primary outcome was the prevalence of pre-transplant CAD and its impact on LT outcomes. Secondary outcomes include the cardiovascular outcomes post-transplant for patients with CAD pre transplant, and frequency of new onset CAD post-transplant. Post-transplant CVD was defined as the occurrence of one or more of the following; development of further episode of CAD, heart failure, arrhythmia and/or stroke as identified in electronic medical records by the treating physician. Cause of death was ascertained using hospital discharge letters and death certificates.

3.3.3 Statistical analysis

Descriptive statistics were performed using median (interquartile range, IQR) for continuous variables and frequency (percentage) for categorical variables. Comparison for categorical variables was performed using chi-squared test of independence. All p-values are two-tailed with $p < 0.05$ considered statistically significant and p-values were provided to three decimal places.

3.4 Results

3.4.1 Patient demographics

During the study period, there were 366 patients assessed for LT. Pre-transplant CAD (defined as any patient with a history of myocardial infarction or obstructive coronary disease with or without revascularisation) was present in 22 patients. There were 15 patients who had known CAD prior to LT assessment, while the remaining 7 patients were diagnosed with CAD during their LT assessment. Demographic data is summarised in Table 3.1. Except for one patient with a non-cirrhotic indication for LT (neuroendocrine liver tumour - insulinoma), all LT candidates had cirrhosis. MAFLD was the most common aetiology of liver disease in these patients, followed by alcohol related liver disease. Over half of all patients with pre-transplant CAD had at least one identified cardiovascular risk factor, and 15 LT candidates had at least 2 identifiable cardiovascular risk factors (Table 1). No patient had a normal BMI and 10 patients (45%) met the definition of obesity (BMI $>30 kg/m^2$). Information on dyslipidaemia and family history were not routinely available.

Table 3.1: Demographic data in patients with pre-transplant CAD

(n=22)	
Age (median, IQR) years	62 (8)
Male, n (%)	20 (92)
MELD, median (IQR)	14 (8)
Na-MELD, median (IQR)	17 (8)
Hypertension, n (%)	12 (55)
DM, n (%)	10 (45)
Smoking, n (%)	13 (59)
BMI, median (IQR)	31 (8)
CAD diagnosed pre-LT assessment, n (%)	15 (68)
Cardiac dysfunction, n (%)	16 (73)
Aetiology of cirrhosis, n (%) **MAFLD** **Alcohol** **Hepatitis B/C** **Autoimmune**	 9 (43) 8 (38) 2 (10) 2 (10)

3.4.2 Cardiac investigations in patients with pre-transplant CAD

3.4.2.1 Electrocardiograms

There were four patients with abnormal ECGs, including one patient with atrial fibrillation, one patient with bundle branch block, one patient with bradycardia, and one patient with AV block. QT prolongation was also highly prevalent, found in 10 patients (45%). No patient developed

complications of QT prolongation such as polymorphic ventricular tachycardia or sudden cardiac death.

3.4.2.2 TTEs

The results of resting TTE for patients with pre-transplant CAD included median LVEF (IQR) 65% (6). Sixteen patients (73%) had DD, of which the majority was grade 1-2 DD, while two patients had severe, grade 3 DD. The median LAVI (IQR) was 28.5 (14) and the median E:e' (IQR) was 11 (11).

3.4.2.3 DSE

Among 365 LT candidates assessed with DSE, the target heart rate was achieved in 17 (77%) cases, with poor image quality hindering diagnostic accuracy in one case. One patient did not undergo DSE due to medical instability and a recent acute coronary event, therefore they proceeded directly to CA. It was not possible to explore sensitivity and specificity of DSE as "gold standard" testing with CA, as this was not performed for all patients.

3.4.2.4 Other non-invasive investigations

Only one patient underwent CTCA as part of the LT workup, with mild coronary atherosclerosis detected. No patient underwent cardiac MRI or CT coronary artery calcium score.

3.4.2.5 CA and revascularisation procedures

Out of the 22 patients with CAD only 10 underwent CA, with results summarised in Table 3.2. There were no observed complications of CA or revascularisation in our cohort. Of all patients that required CA, obstructive lesions were seen in four patients. Due to coagulopathy, two patients received bare metal stents to minimise duration of anti-platelet agents. Due to a high-level obstruction seen in the

left main artery and comorbid DM, one patient underwent CABG. The one patient who underwent CABG had MELD score of 14 and minimal significant coagulopathy. Furthermore, he had a proximal left main coronary artery stenosis where PCI was deemed insufficient to clear his heart for LT. Thus after multi-disciplinary review, we proceed with the decision to proceed with CABG rather than PCI. All revascularisation procedures happened as the final step prior to listing for transplantation. Both patients that had PCI revascularisation were successfully transplanted, and the LT candidate who underwent CABG survived and remains on the LT waitlist.

Two patients with an obstructive lesion on CA, and all patients with mild CAD received medical therapy in the form of statins, antihypertensives and antiplatelet agents. No patient was declined LT listing due to CAD alone.

Table 3.2: Findings on CA in LT candidates

Outcome of CA	**N**
Mild CAD	3
Mild-moderate CAD	3
Obstructive lesion	4
Normal	
Revascularisation	
PCI	2
CABG	1

3.4.3 Pre-transplant morbidity and mortality

Pre-transplant morbidity is defined as ≥3 hospital admissions. This was observed in 14 (64%) of patients. AKI or HRS was observed in 11 (50%) of patients. There were 8 patients that died without LT, and the causes of death include 6 due to decompensated liver disease and sepsis, 1 patient had a large variceal bleed, and 1 patient had a sudden cardiac death at home.

3.4.4 Liver transplantation

Thirteen patients proceeded to LT during the study period. One patient remains on the LT waitlist after successfully undergoing CABG.

3.4.5 Peri-operative and post-transplant morbidity

Of the thirteen patients who proceeded to LT, 8 (62%) experienced peri-operative morbidity; including AKI (2 patients), rejection (5 patients), and one patient also had severe PPHTN and cardiac failure, requiring epoprostanol infusion immediately post-transplant.

Post-transplant cardiovascular events occurred in six patients (53%), within a median period (IQR) of 1.4 (2.9) years. One patient had both heart failure and a new arrhythmia requiring hospitalisation. The earliest event was a patient being diagnosed with heart failure approximately 3 months post-transplant. Reassuringly, no early (<1 month) ischaemic events occurred in our cohort (Table 3.3).

Table 3.3 Post-transplant cardiovascular events in patients with pre-existing CAD (n = 6)

	Early post-transplant CVD (<1 year)	Late post-transplant CVD (>1 year)
CAD, n (%)	1	1
Heart failure, n (%)	2	1
Arrhythmia, n (%)	0	1
Stroke, n (%)	0	0
Sudden cardiac death, n (%)	0	1
All cardiovascular death, n (%)	0	0

3.4.6 New onset post-transplant CAD

New onset post-transplant CAD occurred in 4 patients. All patients had a smoking history. The patient who underwent CABG post-transplant also had known longstanding diabetes, present prior to LT. These patients had no evidence of CAD detected during their transplant workup. The earliest new-onset event was 2 months post-transplant in a patient presenting with unstable angina. Table 3.4 summarizes the new onset CAD events in LT recipients without diagnosed pre-transplant CAD, with all events occurring within 5 years of LT despite routine management of post-transplant cardiovascular risk factors.

Table 3.4 Post-transplant cardiovascular outcomes in patients with new onset post-transplant CAD

	Event	Time post-transplant
Patient 1	Unstable angina	2 months
Patient 2	STEMI	2 years
Patient 3	Exertional angina	2 years
Patient 4	3 vessel disease > CABG	5 years

3.4.7 Post-transplant mortality

There were 3 deaths recorded in our cohort with pre-transplant CAD, with overall survival of 77% up to 10 years post-transplant. Two deaths occurred in the context of severe sepsis from hepatic abscesses despite broad spectrum antimicrobial therapy, one of these patients had chronic rejection. Neither of these patients had a confirmed hepatic artery thrombosis. The third death was due to sudden cardiac arrest, occurring 3.5 years post-transplant.

3.5 Predictors of post-transplant adverse outcomes

Post-transplant CVD (defined as heart failure, CAD, stroke or significant arrhythmia) was significantly more prevalent in patients with pre-transplant CAD, ($p = 0.00024$). Over 50% of patients with pre-transplant CAD had a further cardiovascular diagnosis following LT, compared to 9.8% in those without pre-transplant CAD. Having CAD pre-transplant, regardless of need for intervention, was not associated with overall post-transplant l mortality ($p = 0.823$).

3.6 Discussion

Recent studies have highlighted that CVD is highly prevalent in in LT candidates, and substantially contributes to early post-transplant morbidity and mortality (119, 272). We present a retrospective

review of patient outcomes with pre-transplant CAD in our state-wide LT centre. In our cohort, no candidate was declined LT due to CAD alone, and three patients underwent revascularisation procedures pre-transplant with no immediate complications. There was no cardiovascular morbidity or mortality events in the first 30 days post-transplant. Long-term, post-transplant CVD was highly prevalent (>50%) in LT recipients with pre-transplant CAD.

The overall pooled prevalence of CAD in liver transplant candidates was 15.9% in a recently published systematic review of CAD in LT recipients (150). This prevalence data was based predominantly on retrospective studies. In comparison, the prevalence in our cohort was 7% over 10 years. MAFLD was the primary cause of liver disease in nearly half of LT candidates with CAD in our cohort. Alcoholic liver disease was the second most common cause of liver disease in this cohort, with a recent longitudinal study confirming patients with alcoholic liver disease have increased rates of CVD (273). Studies have also highlighted that certain risk factors, including DM, age and MAFLD, were correlated with a high risk of clinically significant CAD in LT candidates (7, 77, 88, 158). MAFLD is increasingly recognised as an independent risk factor for obstructive CAD, independent of the presence of other risk factors (157, 158). Furthermore, pre-transplant DM is associated with adverse post-transplant survival (144, 188). Despite these 22 patients being inherently high risk given the pre-existing CAD diagnosis, not all patients received anatomic assessment of their coronary arteries. Whilst there was no significant difference in the rate of CVD in patients who did not undergoing anatomic assessment, this is considered an unmet need in this population. Caution must be placed on making major conclusions from this study given the very small patient numbers. Possible explanations for why routine coronary angiograms were not routinely done include theoretical concerns regarding coagulopathy and AKI raised by cardiology at the time, limited radiology access to CTCA 5-10 years ago, and limited awareness of the importance of diagnosing and treating CAD

in these patients pre-transplant. A risk stratified approach to LT candidates can help rationalize which investigations are necessary and improve post-transplant outcomes, particularly for high-risk patients with multiple cardiovascular risk factors and known pre-transplant CAD. Implementation of this absolutely requires an update of the cardiac workup to be adopted by cardiology, hepatology, and anaesthesiology systematically.

DSE was performed in the majority of LT candidates with pre-transplant CAD, and further investigations including CTCA or invasive CA were performed at the discretion of the consulting cardiology team, despite the high risk nature of this cohort. The target heart rate was only achieved in 77% of DSEs performed. The sensitivity of DSE in cirrhosis is hindered by hyperdynamic circulation, chronotropic incompetence and beta-blocker use, contributing to inconclusive or false negative studies (7, 88, 89). Our current standard of practise at SALTU complied with the 2012 AHA guidelines to commence with non-invasive stress testing (194), and the AASLD guidance on pre-transplant workup (147). Since the publication of these guidelines, systematic reviews have reported poor sensitivity of DSE (35–37%) in detecting significant CAD in cirrhosis (90). Furthermore, case series have demonstrated that DSE failed to predict major cardiovascular events post-transplantation (7, 274). CTCA has been endorsed as a superior alternative in non-invasive testing for CAD in LT candidates (89, 213). CTCA is highly sensitive, requires minimal contrast, and is strongly predictive of early post-transplant CAD events if positive (217). Mild-moderate CAD identified on CTCA allows identification of patients who would benefit from intensified treatment of cardiovascular risk factors.

A recent international study of patterns of practise highlighted that only 13% of transplant centres had a management protocol for CAD diagnosed during transplant workup (275). Some transplant

centres proceeded directly to invasive CA among all patients with pre-transplant CAD (33, 152). Despite the high-risk nature of our cohort, CA was only performed in 9 patients, and most patients with pre-transplant CAD did not undergo any other form of anatomic testing of their coronary arteries. When significant CAD was detected, revascularisation was only undertaken in 3 of 7 patients. Earlier studies did not demonstrate improvement in post-transplant survival with revascularisation of CAD (77, 201). Since then, recent case series have demonstrated that revascularisation is strongly supported by comparable survival outcomes to LT candidates without CAD, and very low complication rates in the setting of radial access and newer drug eluting stents that require shorter periods of dual anti-platelet therapy (7, 152, 248). Of note, the timing of revascularisation, if deemed appropriate, should only occur as the final step prior to listing a patient. Lesions seen on CTCA can be used to guide need for invasive CA and revascularisation required prior to LT (89). In our cohort, CTCA was only offered once among the 22 patients with known CAD pre-transplant. Increased utilisation of CTCA will provide a safer, less invasive option to LT candidates moving forward.

Reassuringly no post-transplant cardiovascular morbidity and mortality was observed in our patients in the first 30 days post-transplant. Other studies found a correlation between pre-transplant CAD and increased post-transplant mortality (252). Koshy et al. recently reviewed the early and late post-transplant cardiovascular mortality over 30 years in Australia (2). They found that despite overall improvements in LT outcomes, the 30-day mortality of LT continued to be 2.3%, similar to the risk open heart surgery, with a substantial proportion attributed to CVD (2). Furthermore, a recent systematic review and meta-analysis found that the mortality rate in patients with pre-transplant CAD was 8.1%, and that cardiac-related mortality made up 0.8% of causes of death (150). It was demonstrated that pre-transplant CAD was a risk factor for both overall (OR 1.4, 95% CI 1.4-1.4, p = 0.01) and cardiac-related mortality (OR 1.2, 95% CI 1.1-1.3, p=0.03) (150). These findings

reinforce the need for comprehensive pre-transplant CAD screening and aggressive management of cardiovascular risk factors in all LT recipients.

The weaknesses and limitations of this study is primarily driven by the small case numbers. This reflects the size of the relatively small size of the South Australian liver transplant Unit and the selection bias introduced by most of these LT candidates being free of significant comorbidities in order to be considered for LT in the first place. Furthermore, clarification regarding pre-transplant cardiovascular risk factors was often incompletely documented on retrospective review, making a full cardiovascular risk profile difficult on these patients. This study has also highlighted the need for a multi-centre study of all patients with both compensated and decompensated liver disease, and to assess the clinical outcomes following coronary angiography and revascularisation. This will allow inclusion of a larger cohort of patients outside those patients who are considered LT candidates alone. Furthermore, this will provide insight into the procedural risk of AKI, vascular access issues, and stent failure, in addition to the post procedural issues of significant gastrointestinal bleeding and mortality. Such a study has the potential to enrich the area of CAD in the cirrhotic population who have been largely excluded from cardiovascular studies historically.

3.7 Conclusion

Pre-transplant CAD was seen in 50% of patient with MAFLD and alcohol related liver disease. Appropriate revascularisation of significant CAD was undertaken. Despite this, post-transplant CVD was common in patients with pre-transplant CAD. Adoption of acardiac risk stratification tool for CAD is necessary to optimise cardiac outcomes post-transplant (88).

Chapter 4: Proposed changes in the cardiac workup of LT candidates in SALTU

4.1 Current standard of practise at SALTU

All LT candidates require a thorough cardiac evaluation given the adverse impact of CVD on pre and post-transplant morbidity and mortality. At present, cardio-pulmonary assessment in SALTU includes history, examination, lipid profile, blood glucose, HbA1c, 12- lead ECG, TTE, DSE, chest x-ray, pulse oximetry, pulmonary function testing, and cardiopulmonary exercise testing. These investigations exclude the presence of any prohibitive cardiopulmonary diseases. The guidelines recommend further review and workup of patients with significant risk factors for cardiac and pulmonary diseases. Summarised below are the recommendations from pages 12-16 of the SALTU handbook, version September 2020, summarised in Table 4.1.

Table 4.1: Workup for different cardiopulmonary diseases in LT candidates at SALTU

Possible CVD	DSE abnormality guides need for CA – 3rd gen DES with minimum DAPT time of 4-6 used
Possible HPS	Arterial O2 <40mmHg associated with unacceptable operative risk
Possible PPHTN	Screen with TTE (ePAP, RVSP, RA volume, RV hypertrophy) If present and responds to vasodilator therapy, needs mPAP <35mmHg and PVR < 5 Wood Units to be suitable for listing Early Swan-Ganz prior to anaesthetisation peri-procedurally to ensure operation can proceed

Currently, notable areas of inquiry with regard to cardiopulmonary assessment in SALTU relate to the following areas:

- CAD workup, for those with multiple cardiovascular risk factors utilising CTCA and CA with less reliance on DSE and in accordance with the emerging evidence
- Evaluation for CCM applying the new criteria

4.2 Patterns of practice in cardiac workup of LT candidates

In a recent American survey of practice patterns in cardiac risk assessment among 61 LT centres, the majority (92%) had a risk-based approach to cardiac assessment (275). A key recognised question in this survey was the nature of cardiovascular risk factors that were considered to guide decision-making in LT candidates. Traditional risk factors such as pre-existing CAD, DM, and advanced age cut-offs were used at 89%, 87% and 84% of transplant centres respectively (275). The presence of MAFLD was used to guide cardiac workup in only 56% of patients, despite previously presented data of MAFLD being a strong predictor of CVD in LT candidates. This is further supported by the findings of a recent systematic review and meta-analysis, which confirmed that traditional cardiovascular risk factors were all strong predictors of pre-transplant CAD, in addition to MAFLD (OR 2.4, 95% CI 14.-4.3, p = 0.02) (150). Hepatitis B infection and hepatocellular cancer were also found to be statistically significant predictors of pre-transplant CAD in this meta-analysis, with odds ratios of 1.4 and 1.6 respectively).

In terms of testing modality, despite mounting evidence for the shortcomings of DSE, it was the most common (80%) non-invasive modality used to assess myocardial function and risk of latent CAD followed by SPECT (49%), CTCA (30%), and exercise stress testing (28%) (275). Finally, while routine TTE was common, use of tissue Doppler myocardial imaging was much lower (13%), despite

the correlation between GLS and post-transplant CVD (89). There was also a difference in pre-transplant workup across continents, with European transplant centres favouring a combination of both functional and invasive coronary artery testing, whereas North American centres relied on either anatomic or functional cardiac testing alone (150). Some centres routinely performed invasive CA as part of their LT workup. Optimal medical therapy of pre-transplant CAD resulted in comparable outcomes to patients without CAD (9, 152).

4.3 Existing cardiac protocols for LT candidates

A recent clinical review of cardiovascular and pulmonary workup of LT candidates in North America recommended that stress testing alone should no longer be used for risk stratification or detection of significant CAD, or prediction of cardiovascular events in LT candidates (33). Instead, coronary angiography (either using CT or invasively) is the new evidence-based standard of care for detection of latent CAD in LT candidates. Robertson et al. published results of their protocol of cardiac assessment involving 569 LT candidates; the largest prospective study published to date (88). They divided patients' cardiovascular risk based on age, DM and previous history of CAD. Depending on risk, patients were assigned to either TTE, DSE or DSE and CTCA (Figure 4.1).

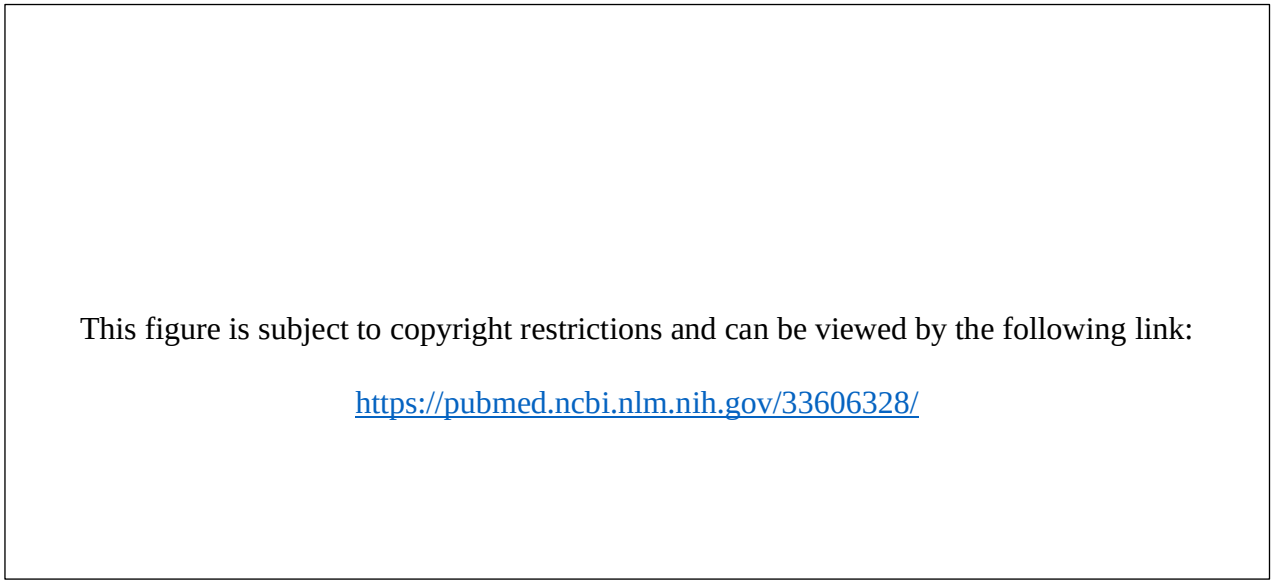

Figure 4.1: A 3-tiered cardiac risk stratification protocol with standardised investigations. Additional cardiac risk factors included hypertension, smoking, first-degree relative with CAD, and hypercholesterolemia. CTCA, cross sectional coronary angiogram; DSE, dobutamine stress echo; HR, high risk; HRCC, high risk cardiology clinic; IR, intermediate risk; LR, low risk; TTE, trans thoracic echocardiogram Reproduced from reference (88)

This algorithm resulted in low rates of 30 day post-transplant morbidity and mortality (1.2% and 0.4% respectively) (88). Furthermore, 12 patients were precluded from LT based on sequential imaging investigations and expert cardiology input due to their cardiovascular comorbidities. 44 of the 173 CTCAs performed showed abnormal cardiovascular anatomy. Only two cases proceeded to revascularisation pre-transplant in Robertson et al.'s study. Regardless, the detection of mild to moderate CAD that does not require revascularisation is no less important than a critical stenosis. CTCA can help identify patients with a high burden of coronary atherosclerosis where high-dose statin therapy and other medical therapy is indicated to minimise future risk of plaque events (88). Furthermore, Moon et al. demonstrated that CAD diagnosed using CTCA in LT candidates that did not require intervention was still a predictor of post-transplant myocardial injury and mortality, related to the risk of demand ischaemia and type II myocardial infarction (Figure 4.2) (217).

This figure is subject to copyright restrictions and can be viewed by the following link:

https://pubmed.ncbi.nlm.nih.gov/30653845/

Figure 4.2: Cumulative incidence of type 2 MI stratified by severity of CTCA or coronary artery calcium score in LT recipients. Reproduced from reference (217)

Robertson et al. also shed light on a cohort that has had little recognition until now. In the setting of re-transplantation, patients may develop accelerated CAD in the absence of traditional risk factors. This was demonstrated in their study where 12 re-transplant patients had a post-transplant cardiac event rate of 16.7%, and therefore were considered empirically high risk regardless of cardiovascular risk factors (88).

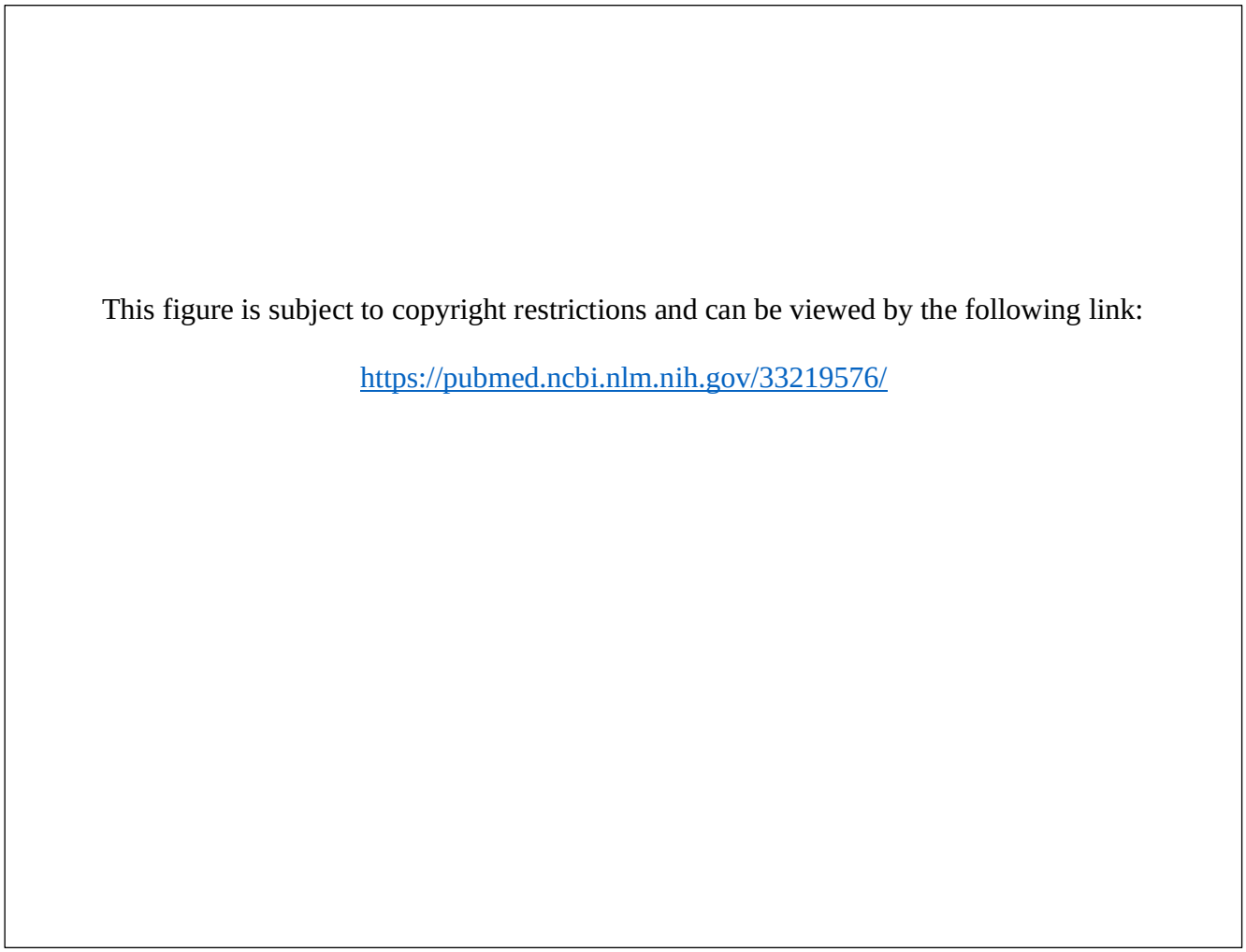

*Figure 4.3: Algorithm for assessment of CAD risk in LT candidates. Abbreviations: LBBB, left bundle branch block; METS, metabolic equivalent of task; RV, right ventricle; TTE, transthoracic echocardiogram. Reproduced from r*eference (89)

In comparison, another recently proposed protocol for post-transplant CVD uses a slightly different approach (Figure 4.3) (89). In this protocol, established CAD is an automatic trigger for specialist cardiology consultation, placing these patients in the high-risk group. Identification of CAD as a high-risk predictor of pre-transplant CVD is strongly endorsed based on previously presented evidence. In comparison, pre-transplant CVD is allocated intermediate risk in the protocol published by Robertson et al. The protocol by Barman et al. recommends that abnormal baseline imaging (electrocardiogram

and echocardiogram) and DM at any age are automatic triggers for CTCA. Other patients are worked up based on their risk factors and particular importance is given to the presence or absence of MAFLD. While both diagnostic algorithms increase chances of detection of significant CAD pre-LT, there is no consensus among centres in this regard. Barman's protocol is simpler, with less reliance on arbitrary cut-offs for age and decision making based on the strongest cardiovascular risk factors.

4.4 Refining pre-transplant cardiac assessment in SALTU4.4.1 Risk factors in the workup of CVD in LT candidates

The cardiovascular assessment in LT candidates should begin with a thorough history and clinical examination assessing risk factors such as smoking, hypertension, dyslipidaemia and strong family history, followed by investigations according to the specific cardiovascular risk of the patient (189). The importance of recognition of existing cardiovascular risk factors to gauge cardiovascular risk pre-transplant is critical. In addition, non-traditional cardiovascular risk factors in the LT candidate such as MAFLD and renal dysfunction need to be considered during LT assessment.

4.4.2 The current role of DSE

There is consensus among existing protocols that DSE serves best as a screening method only for the low-risk cohort. This is also reflected in the CAD-LT risk score calculator produced by Rachwan et al. (198). Despite the low sensitivity, the role of DSE cannot be completely ignored. De Gasperi et al. highlighted that in addition to the presence of coronary calcifications, the ability to induce myocardial ischaemia is important to guide the need for revascularisation in LT candidates (219). DSE continues to be a simple method of functional coronary testing that can complement CTCA or coronary artery calcium scoring, in addition to its importance in assessing myocardial reserve in the

setting of CCM and predicting HRS (70). Hence our proposed diagnostic pathway should include DSE in all patients considered for LT.

4.4.3 Including CTCA in the diagnostic armamentarium

CTCA requires the presence of an expert radiologist for non-coronary findings in addition to a cardiologist for the coronary report. The risk of abnormal CTCA increases with age and the presence of DM, as demonstrated in the general population (214). By utilising CTCA in the LT cohort, we anticipate an increase in diagnosis of coronary atherosclerosis, in line with the increasing comorbidities of LT candidates that is being observed. Using CTCA to detect high risk lesions that require consideration of revascularisation is crucial to the success of overall LT outcomes. CTCA has been demonstrated as a safe and highly sensitive method for investigating significant CAD in LT candidates (217). CTCA is non-invasive and has a comparable detection rate of significant CAD to traditional CA, with potential for measuring fractional flow reserve (and thus functional significance of a detected lesion) (150). A retrospective study of over 2,000 LT candidates found that those with 2 or 3 vessel disease on CTCA screening had a 4.9 times higher risk of post-transplant myocardial infarction within 30 days of LT (217). The prognostic role of CTCA in post-transplant CVD needs to be studied further.

CA has been proven to be safe in LT candidates. However, resource allocation for detecting clinically significant CAD is a significant consideration. Focusing on CTCA for the majority of LT candidates will limit utilisation of CA to those with abnormal coronary calcification or very high risk of underlying CAD (such as those with three vessel disease or left main artery disease) (22). Although studies have employed platelet count of $<20 \times 10^9$L or INR >2.0 as indications to correct

coagulopathy (9), thromboelastometry prior to CA and transradial CA will result in judicious blood product replacement, whilst ensuring that bleeding risk is minimised.

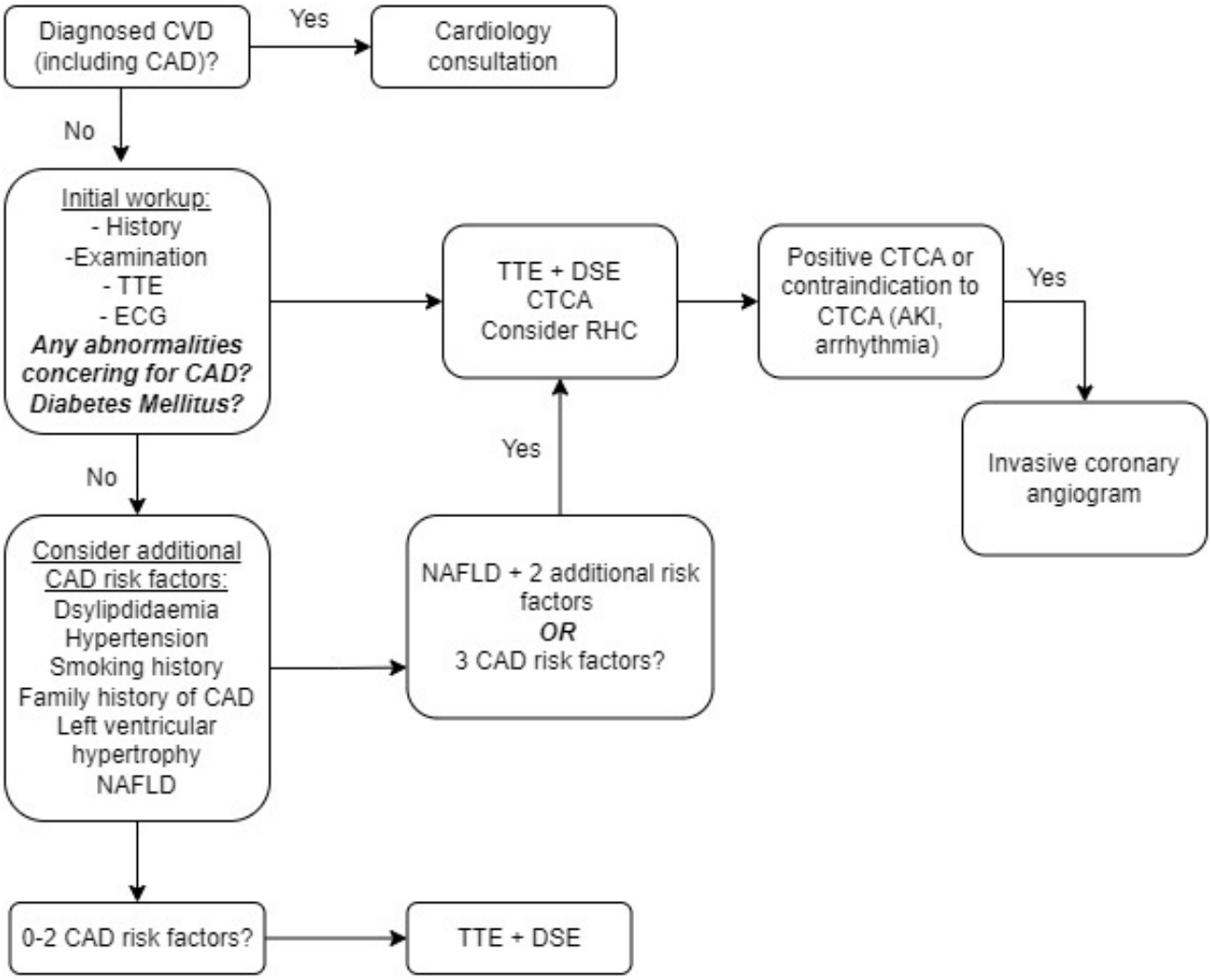

Figure 4.4: Proposed algorithm for assessment of CAD risk in LT candidates for SALTU. Abbreviations: AKI, acute kidney injury; CAD, coronary artery disease; CVD, cardiovascular disease; CTCA, computed tomography coronary angiogram; DSE, dobutamine stress echocardiogram; ECG, electrocardiogram; MAFLD, non-alcoholic fatty liver disease; RHC, right heart catheterisation; TTE, transthoracic echocardiogram.

4.4.4 Proposed assessment for CAD in LT candidates

We suggest employing a similar protocol at SALTU to those described above (Figure 4.4). This protocol takes reference from Barman's protocol with particular attention to the comprehensive risk factors that are considered in addition to DM and MAFLD. To aid in the flow of the algorithm in Figure 4.4, specific diagnostic criteria are presented as follows:

- DM: Fasting blood sugar level of 7mmol/L or higher on two occasions, abnormal oral glucose tolerance test, or Hba1c above 7% without recent blood transfusion (276)
- Dyslipidaemia: Lipid profiles are not accurate in the setting of end-stage liver disease, pre-liver failure cholesterol studies should be reviewed, particularly low density lipoprotein >1.4mg/L (202)
- Hypertension: systolic blood pressure above 140mmHg or diastolic blood pressure above 100mmHg (276)
- Left ventricular hypertrophy: diagnosed on TTE or MRI (276)

An additional factor to be considered is the need for yearly review of CVD and repeat TTE +/- DSE for those patients that remain on the waitlist for extended periods, as supported by VanWagner et al. (33).

We plan to present this protocol to the consulting cardiology team at SALTU, with the aim of adopting this process in our unit. The utilisation of a risk factor guided approach, agreed upon by anaesthesia, cardiology and the hepatology specialty teams, will allow a thorough workup of LT candidates. A notable downside will be an increase in resources needed to meet the demand of CTCA, in addition to potential CA and revascularisation. This is offset by the significantly higher sensitivity and specificity of these tests, therefore allowing multidisciplinary intervention of any underlying CAD to optimise the patient pre-transplant. Following implementation, we propose a prospective

study of cardiovascular outcomes of liver transplant candidates. The specific outcomes that we would observe include the following:

- Rate of complications post coronary angiography (with or without PCI), including AKI and bleeding. An important issue this should address is the specific management of high risk coronary lesions in decompensated cirrhosis. The rationale for this being that after PCI, this will place patients on hold from listing for up to 3 months,, which is severely decompensated cirrhosis may be prohibitively high a risk.
- The incidence and management of cardiovascular events in the immediate, short term and long term post-transplant period. Specific issues to explore should include the value of regular echocardiography plus stress testing post-transplant in patients with multiple risk factors for CVD. We propose a case control study with another transplant centre where regular echocardiography is not routinely performed. The rationale for this study is that regular TTE is increasingly recommended in guidance statements by international experts but lack high-level supporting evidence.
- Multi-centre comparators to allow external validation of the SALTU clinical outcomes by combining data with another LT centre with a cardiovascular workup protocol. This is best achieved by having similar protocols across LT centres in Australia, and as such escalation of discussion to the Liver and Intestinal Transplant Advisory Committee to have a unified, standardised transplant cardiovascular protocol across Australia.
- An updated systematic review is also recommended of the incidence of CVD and post-transplant morbidity and mortality as there has been a sharp rise in published literature in the past 5 years.

4.5 Conclusion

Using the proposed coronary risk stratification model, LT candidates can be more appropriately investigated for CAD to guide operative risk and subsequent management of cardiovascular risk factors. Development of protocols supported by hard clinical outcomes is crucial to standardizing the cardiovascular workup in LT candidates. CTCA offers an excellent non-invasive approach to assessment of CAD reserving invasive CA for those who require revascularisation. Should revascularisation be required, clinical outcomes post-transplant are similar to those patients without pre-transplant CAD. Prospective studies are essential to assess the outcome of these diagnostic pathways in improving the diagnosis and management of CAD in LT candidates.

Chapter 5: Summary and Recommendations

5.1 Summary

Cardiovascular disease (CVD) in LT candidates is increasingly recognised as a leading cause of morbidity and mortality both before and after transplantation (1, 2). The increasing prevalence of MAFLD in LT candidates carry with them an inherently high likelihood of myocardial dysfunction and CAD, making cardiac risk an important consideration in pre-transplant evaluation (6, 7). There is an unmet need for cardiac re-modelling treatments in patients with heart failure, and safe revascularisation of CAD in cirrhosis. Oftentimes however, the liver failure is so far advanced that most cardiac therapies are considered unsafe. In addition, advanced liver disease is also associated with intrinsic cardiac dysfunction such as CCM, which contributes to poorer prognosis. Due to the unique circulatory changes of cirrhosis, cardiac dysfunction is largely subclinical and hence early recognition and watchful management are essential.

Provided the patient is deemed suitable for LT, close cardiology follow-up post-transplant becomes pertinent to their longevity. This was demonstrated in Chapter 2 of this thesis, which examined the impact and prevalence of cardiac dysfunction on pre- and post-transplant outcomes in SALTU (81). The study revealed its high prevalence (58%) and significant role in renal dysfunction pre-transplant, peri-operative and post-operative overall morbidity.

The overall pooled prevalence of CAD pre-transplant was 15.9% in a recently published systematic review of CAD in LT recipients (140). Despite advances in surgical techniques and improved immunosuppression, the risk of post-transplant CVD remains considerable, with prevalence rates up to 30% among LT recipients (151). This is further influenced by the increasing prevalence of MAFLD, and the consequent increase in metabolic syndrome and CAD (8, 9). In our cohort, similar

to other studies, pre-transplant CAD was not prohibitive to LT. There is increasing real world evidence that CAD be managed with coronary revascularisation in patients with advanced cirrhosis with an acceptable rate of complications, which is supported by the findings presented in this thesis. We also found that anatomic assessment of coronary arteries either invasive or using CT was underutilised, and requires optimisation to reach the standard that is being set internationally. Whilst our patients were successfully revascularized, the presence of CAD pre-transplant was significantly associated with the development of cardiovascular events post-transplant. A cardiac risk stratification tool in accordance with recent literature should be implemented to optimise cardiac outcomes post-transplant in anticipation of the impending increase in LT candidates at risk of CAD.

5.2 Recommendations for the management of cardiovascular disease in cirrhosis

The CCM consortium has proposed new diagnostic criteria incorporating advanced echocardiographic parameters (GLS and tissue Doppler parameters for advanced DD) to detect subclinical cardiac dysfunction that is characteristic of CCM (5). We suggest routinely evaluating for CCM by reporting on these parameters during cardiac evaluation for all patients with advanced cirrhosis, including pre-TIPSS and pre-transplant. Prospective studies assessing these parameters before and after cardiac dysfunction and better understanding of their clinical significance are currently being undertaken in our unit (269). Multicentre studies using cardiac MRI, GLS and stress echocardiography before and after LT are required to understand the structural, functional and clinical significance and reversibility of CCM.

CAD continues to be a common cardiac condition complicating both early and late post-transplant care for LT recipients (2, 238). Comprehensive, standardized cardiovascular workup including that for CAD in LT candidates is crucial to improving post-transplant cardiovascular outcomes. This

thesis has methodically presented the historical approaches to CAD in LT candidates, as well as the benefits of a risk factor based evaluation for CAD using CTCA and invasive CA as discussed in Chapter 1 and 4. Multidisciplinary care with regular cardiology review is necessary for these patients, including the post-transplant period. Once this has been established, it would be prudent to investigate the clinical outcomes in SALTU with a follow up audit of the cardiovascular outcomes in LT recipients in South Australia. Finally, exploration of a nationwide approach to cardiovascular work-up in LT with the Liver and Intestinal Transplant Advisory Committee of the Transplantation Society of Australia and New Zealand is also proposed, as the best means of applying state-of-the-art evidence based care standardised across the entire Australian LT community.

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