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COMPREHENSIVE REVIEW

Management of cardiac diseases in liver transplant recipients: Comprehensive review and multidisciplinary practice-based recommendations

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Cardiac diseases are one of the most common causes of morbidity and mortality following liver transplantation (LT). Prior studies have shown that cardiac diseases affect close to one-third of liver transplant recipients (LTRs) long term and that their incidence has been on the rise. This rise is expected to continue as more patients with advanced age and/or non-alcoholic steatohepatitis undergo LT. In view of the increasing

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; AST, American Society of Transplant; BB, b-adrenergic receptor blocker; CAC, coronary artery calcium; CHD, coronary heart disease; CKD, chronic kidney disease; CT, computed tomography; DCCV, direct-current cardioversion; DM, diabetes mellitus; DOAC, direct oral anticoagulant; ECG, electrocardiogram; HF, heart failure; LICOP, Liver and Intestine Community of Practice; LT, liver transplantation; LTR, liver transplant recipients; MI, myocardial infarction; NASH, non-alcoholic steatohepatitis; NDCCB, non-dihydropyridine calcium channel blocker; RCT, randomized controlled trial; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; VHD, valvular heart disease.

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disease burden, a multidisciplinary initiative was developed to critically review the existing literature (between January 1, 1990 and March 17, 2021) surrounding epidemiology, risk assessment, and risk mitigation of coronary heart disease, arrhythmia, heart failure, and valvular heart disease and formulate practice-based recommendations accordingly. In this review, the expert panel emphasizes the importance of optimizing management of metabolic syndrome and its components in LTRs and highlights the cardioprotective potential for the newer diabetes medications (e.g., sodium glucose transporter-2 inhibitors) in this high-risk population. Tailoring the multidisciplinary management of cardiac diseases in LTRs to the cardiometabolic risk profile of the individual patient is critical. The review also outlines numerous knowledge gaps to pave the road for future research in this sphere with the ultimate goal of improving clinical outcomes.

KEYWORDS
cardiac outcomes, cirrhotic cardiomyopathy, coronary artery disease, liver transplant

1 | INTRODUCTION

Cardiac disease is a common cause of morbidity and mortality after liver transplantation (LT).[1] Specifically, cardiac disease is noted to be one of the three main causes of non-graft-related death after liver transplant in two long-term observational studies, contributing to 12% of deaths in one study from the United States[2] and 19% in another study from Europe.[3] Furthermore, the cumulative incidence of cardiac disease is as high as 30.3% in LT recipients (LTRs) within 8 years post-LT.[4] With improved LT-related care, LTRs are living longer and more patients with advanced age (> 65 years old) are undergoing LT.[5] Importantly, the proportion of patients undergoing LT for non-alcoholic steatohepatitis (NASH) has been steadily increasing around the world.[6,7] Because both older age and NASH are highly associated with post-LT cardiac disease, the absolute risk for post-LT cardiac disease at this time is likely higher than what had been previously reported in older studies from the 1990s and early 2000s.[1-4] To this end, a recent study, using a national US inpatient database, showed that the rates of hospitalization for post-LT cardiac disease increased by 115% between 2002 and 2011.[8] The study also noted an uptrend in heart failure (HF) and arrhythmia and a downtrend in coronary heart disease (CHD).[8] Notably, a recent meta-analysis showed that post-LT cardiovascular disease in patients transplanted for NASH is not significantly different from that in patients transplanted for other diseases. This may suggest that post-LT de novo cardiovascular risk factors can blunt the difference in cardiovascular risk between NASH and others; an observation that calls for special attention to those de novo risk factors.[9]

The aforementioned findings highlight the need for an individualized approach to optimizing the care for each of the cardiac disease entities among LTRs to improve clinical outcomes and prolong the utilization of a scarce organ. In November 2019, a multidisciplinary group of North American experts from transplant hepatology, transplant cardiology, transplant nephrology, and transplant pulmonology met in a consensus conference focused on cardiac disease management in non-cardiac solid organ transplant recipients, that was sponsored by the American Society of Transplant (AST) and held in Washington, D.C. Subsequently, an initiative was developed to critically review the existing literature and formulate practice-based recommendations on cardiac risk assessment and risk mitigation *specifically* as it relates to LTRs at high risk for or have the following cardiac diseases: CHD, HF, arrhythmia, and valvular heart disease (VHD). Based on this initiative, in this review, we outline the epidemiology, diagnosis and management approach as well as practice-based recommendations for each of these cardiac disease entities.

2 | MATERIALS AND METHODS

The literature search, conducted by a medical librarian, included peer-reviewed articles that were randomized controlled trials (RCTs), narrative reviews, systematic reviews and meta-analyses, or observational studies. PubMed, EMBASE and Cochrane databases were queried for English language papers published between January 1, 1990 and March 17, 2021. The search keywords are outlined in Data S1. Case series and case reports were excluded. The multidisciplinary writing group was divided into four expert panels addressing each of the four cardiac disease entities. The literature surrounding each of these entities was comprehensively assessed and discussed by the respective expert panel in the form of a series of conference calls. Summary statements for each topic were then developed and presented to the entire group, revising each statement as needed until a final version was agreed on by all members of the writing group. The level of evidence for all statements was graded using the Oxford Centre for Evidence-based Medicine Levels of Evidence (https://www.cebm.ox.ac.uk/files/levels-of-evidence/cebm-levels-of-evidence-2-1.pdf)[10]

3 | RESULTS AND DISCUSSION

The literature search revealed 385 articles, which were screened for relevance, and 46 additional articles, that were not captured by the initial literature search, were included based on writing group agreement about relevance to cardiac disease in LTRs. Eventually, a total of 184 articles were deemed relevant (Table 1) of which 42 articles revealed data surrounding the epidemiology of cardiac disease in LTRs as summarized in Table 2. The inclusion criteria and outcomes definition for each of these epidemiologic studies are outlined in Data S2. The sections below discuss the epidemiology, diagnosis, and management of cardiac disease in LTRs. The resultant practice-based recommendations, along with the rating of level of supporting evidence, are outlined in Table 3. After rounds of discussion and revision, all the final statements were unanimously approved by the multidisciplinary panel.

3.1 | Coronary heart disease in liver transplant recipients

3.1.1 | Epidemiology

CHD is caused by atherosclerotic plaque-based narrowing or blockage of the coronary arteries. Typically, patients with high-risk coronary lesions not amenable to revascularization are excluded from LT and thus CHD events (e.g., myocardial infarction [MI], acute coronary syndrome or revascularization) are relatively uncommon early after transplant. For example, MI accounts for only ~7% of all cardiac hospitalizations within 90 days post-LT.[8,11] A recent international meta-analysis showed increased cardiac-related mortality in LTRs with pre-existing CHD (i.e., pre-transplant CHD) (1.2 [1.1–1.3]); however, this finding may reflect the overall impact of CHD on variety of cardiac events rather than ischemic events only.[12] The overall prevalence of CHD-related events after LT ranges from 1.3% to 22.7% depending on the population studied and time elapsed since LT (Table 2). In a study from Taiwan, the standardized incidence ratio for CHD was actually lower in LTRs compared with the general population (0.85 [0.62–1.18]), highlighting the fact that the vast majority of cardiac events after LT are non-ischemic in origin.[13]

3.1.2 | Risk factors for post-transplant coronary heart disease

The risk factors for CHD events among LTRs are shown in Figure 1. Notably, older age, prevalent cardiometabolic comorbidities and increasing LT for NASH, coupled with the ongoing effects of long-term immunosuppression contribute to a high long-term risk for CHD events in LTRs.[14-16] Few studies have directly assessed risk factors for CHD events specifically in LTRs and have been fraught by heterogeneity in the definition of cardiac events, small sample size and lack of granular data. For prediction of 10-year CHD risk in LTRs, the Framingham Heart Study score (FRS), Prospective Cardiovascular Münster Study (PROCAM) and Systematic Coronary Risk Evaluation Project (SCORE) showed moderate discrimination with c statistics of 0.707, 0.778 and 0.800, respectively.[17] These findings highlight the potential clinical utility for use of these risk scores to identify LTRs at high risk for CHD events and to guide further prevention strategies.

3.1.3 | Diagnosis, screening, and surveillance for post-transplant coronary heart disease

Screening and surveillance of LTRs for CHD is critical to reducing mortality after transplant. Pretransplant CHD and associated comorbidities can lead to worse LT outcomes.[18] However, the severity of pre-LT CHD, if managed according to guideline-based recommendations, is not predictive of worse post-LT outcomes.[19,20] LTRs who have cardiac events compared with those who do not have been observed to have worse 1-year survival (47% vs. 94%).[21] In LT candidates with suspected CHD, a normal CT coronary angiography can successfully exclude post-LT MI (negative predictive value 97.5%) and identify those who should have follow up invasive coronary angiography to better define the coronary anatomy.[22] Thus, continual clinical surveillance for new or worsening CHD to prevent cardiac events post-LT is reasonable. Non-invasive modalities for assessment of CHD in asymptomatic LT *candidates*, including cardiac CT for coronary artery calcium (CAC) combined with stress echocardiography for the assessment of ischemia, have been shown to predict post-LT CHD events with a sensitivity of 62.5% and specificity of 66.7%.[21] The sensitivity and specificity of these, and other tests (e.g., exercise electrocardiogram), in asymptomatic LTRs is unknown. The frequency of surveillance or monitoring of asymptomatic LTRs is not clearly defined, but close outpatient follow-up, monitoring and

TABLE 1 Reviewed articles summary

Type of cardiac disease	Number of articles screened	Number of relevant articles manually added	Number of relevant articles included
Coronary heart disease	185	34	108
Arrhythmia	68	4	35
Heart failure	81	2	22
Valvular heart disease	51	6	19

surveillance for signs and symptoms of CHD is consistent with the recommendations in the general population.[23] It is also important to consider non-cardiac factors, such as indication for LT (e.g., NASH, hepatitis C, alcohol)[24] and immunosuppression protocols that have been associated with elevated CHD risk (e.g., high dose or prolonged steroids, cyclosporine-based regimens).[25]

3.1.4 | Prevention and management of post-transplant coronary heart disease

Screening for and treatment of hypertension, hyperlipidemia, chronic kidney disease (CKD), diabetes mellitus and tobacco use should occur in all LTRs. However, the optimal method and frequency of testing and treatment remain uncertain. Multiple barriers exist to implement primary and secondary prevention of CHD once identified, including lack of confidence of providers and the complexity of post-LT care.[26] Table 3 summarizes our practice-based recommendations for prevention and management of CHD in LTRs. The rationale supporting these recommendations is outlined in the supplemental material (Data S3).

3.1.5 | Knowledge gaps and future directions to mitigate post-transplant coronary heart disease

Although long-term CHD risk appears significant in LTRs, there remains significant heterogeneity in the available data as to the true prevalence and incidence of CHD-specific risk in this population and optimal screening, surveillance, diagnosis, prevention, and management strategies once disease is identified. Table 4 outlines the high priority areas for future investigation in this critical area to improve the long-term benefit and outcomes among LTRs.

3.2 | Heart failure in liver transplant recipients

3.2.1 | Epidemiology

HF is a clinical syndrome accompanied by imaging evidence of cardiac dysfunction. The reported incidence of post-LT HF is markedly variable depending on the HF definition used and duration of study follow-up (Table 2). On short-term follow-up, the incidence of HF with reduced ejection fraction (HFrEF) ranges from 14% in the first week[27] to 24% within the first 6 months post-LT,[28] but the incidence of HF with preserved ejection fraction (HFpEF) remains unknown within this timeframe. HFrEF refers to a clinical presentation in the setting of left ventricular ejection fraction (LVEF) that is typically <40% while HFpEF refers to a clinical presentation in the setting of LVEF more than 50% with concurrent functional or structural abnormality such as diastolic dysfunction or left ventricular hypertrophy, respectively.[29] Furthermore, in a large single-center study of 1024 LTRs, HF events (based on diagnostic or procedural codes) represented nearly one-third of the cardiovascular events that affected 329 patients within the first year post-LT.[1] Data on long-term development of HF post-LT are limited. Two retrospective studies demonstrated that 10% of LTRs developed HF within approximately 5 years of transplant.[30,31] HFrEF constituted 50% of HF events in one study and 70% in the other study with the rest of events being HFpEF. Interestingly, a recent analysis of a national US database showed that post-LT HF-related hospitalizations in the United States have increased by more than 30% between 2002 and 2011[8] highlighting the importance of devising risk mitigation strategies for HF post-LT.

3.2.2 | Risk factors for post-transplant heart failure

The risk factors for early versus late post-LT HF differ. For example, intraoperative transfusion of >11 units of packed red blood cells and wall motion abnormality on pre-LT transthoracic echocardiography (TTE) were found to be independent predictors of early HFrEF in the first week[27] and in the first 6 months[32] after LT, respectively. However, for long-term development of HF post-LT, the components of metabolic syndrome, which affect more than 50% of LTRs,[33] and the newer diagnostic criteria of cirrhotic cardiomyopathy (CCM), which affects up to 35% of LTRs[30] were found to be independent predictors.[30,31] Moreover, with the rising numbers of older LTRs, the incidence of HF is expected to continue to rise given that advanced age is a well-established risk factor for HF.[34]

3.2.3 | Diagnosis, screening, and surveillance of post-transplant heart failure

Cardiac dysfunction and liver disease often coexist due to systemic disorders and complex cardio-hepatic interactions.[35] CCM is a unique, often subclinical, entity that exemplifies those interactions. CCM diagnostic criteria were recently revised to accommodate the modern developments in echocardiography.[36] These criteria (Figure 2) highlight the importance of comprehensive pre-LT echocardiography. The data about cardiac magnetic resonance imaging (cMRI) in this patient population have started to emerge, but they remain limited.[37] The contemporary definition of HF focuses on the continuum of a clinical syndrome from being at risk of HF to current or prior symptoms or signs of HF.[38] Having CCM, pulmonary hypertension, and/or the metabolic syndrome among other post-LT risk factors can conceivably place LTRs on that continuum. Prompt diagnosis of HF requires awareness of the risk factors in this special patient population and a high clinical index of suspicion along with comprehensive TTE.

With the rising incidence of HF post-LT, close longitudinal cardiac care in high-risk patients is warranted. The data detailing such care are limited. However, for patients with pre-LT cardiac

TABLE 2 Summary of studies describing the epidemiology of cardiac disease after liver transplant

Study (author-year, country)	Design	*N*	Follow-up duration	Cardiac events	CHD	Arrhythmia	HF	Cardiac death
Johnston et al. 2002, UK[90]	Case-control	110	121 months		22.7% at median 30 months			
Borg et al. 2007, Netherlands[91]	Cohort, retrospective	311	Median 6.2 years	11.4%				3.4%
Umphrey et al. 2008, USA[92]	Cohort, retrospective	157	4 months	10%				1.3%
Eleid et al. 2010, USA[93]	Cohort, retrospective	393	4 months	8.8%				
Dowsley et al. 2012, USA[28]	Cohort, retrospective	107	3.2 years				24% in 6 months	
VanWagner et al. 2014, USA[94]	Cohort, retrospective	54,697	30 days					1.2%
Watt et al. 2014, USA[95]	Case-control	798	10 years	8.8% at 4 months 18.4% at 10 years				
Josefsson et al. 2014, Sweden[96]	Cohort, retrospective	234	Mean 4 years			19.5%		
Kong et al. 2015, South Korea[97]	Cohort, retrospective	443	30 days	8.6%				0.6%
Xia et al. 2015, USA[55]	Cohort, retrospective	1387	30 days			7.4%		
Nicolau-Raducu et al. 2015, USA[98]	Cohort, retrospective	389	4.4 years	15.2% at 1 year		3.3% at 1 year		2.8% at 1 year
Weick et al. 2015, USA[99]	Cohort, retrospective	803	5 years	7.8%	5.3%			
VanWagner et al. 2016, USA[52]	Cohort, retrospective	32,810	30 days–90 days	8% at 30 days 11% at 90 days		43% of cardiac events were AF		
Piazza et al. 2016, USA[24]	Cohort, retrospective	143	3 years	7.7% at 1 year 14.1% at 3 years				
Kim et al. 2016, South Korea[100]	Cohort, retrospective	1065	Median 47 months			17.5% during hepatic graft reperfusion, 1.2% with IOAF		
Malik et al. 2016, USA[101]	Cohort, retrospective	146	1.75 years	20.5%				3%
D'avola et al. 2017, Spain[3]	Cohort, prospective	1819	5 years	10.2%				1.7% at 1 year 2.9% at 5 year

TABLE 2 (Continued)

Study (author-year, country)	Design	*N*	Follow-up duration	Cardiac events	CHD	Arrhythmia	HF	Cardiac death
Scholte et al. 2018, Netherlands[102]	Cohort, retrospective	916	30 days	11%		34%		
Moon et al. 2018, South Korea[53]	Cohort, retrospective	1059	N/A			1.2%		
Son et al. 2018, South Korea[103]	Cohort, retrospective	1181	Median 81.9 hours			3.3% new-onset AF		
Chokesuwattanaskul 2018, International[58]	Meta-analysis	38,586	N/A			8.5% post-LT AF		
De Luca et al. 2019, UK[104]	Cohort, retrospective	928	Median 85 months	20.2%		35.3% arrhythmias; 51.5% w/ AF		4.8%
Smilowitz et al. 2019, USA[105]	Cohort, retrospective	49,978 Liver = 10,810	N/A	5.6%	1.3%			
Flaherty et al. 2019, USA[106]	Cohort, retrospective	527	N/A	20.1%	5.9%	7%	2.7%	
Patel et al. 2019, USA[20]	Cohort, retrospective	283	30 days	25.4% at 30 days		20.8% arrhythmias, 9.9% w/ AF		2.1% at 30 days
Siddiqui et al. 2019, USA[107]	Cohort, prospective	130	Mean 66 months		15.4%			
Moon et al. 2019, South Korea[108]	Cohort, retrospective	2118	1 year		2.1%, 3.1%, 3.4%, 4.3%, and 21.4% for normal, nonobstructive CHD, and 1-, 2-, and 3-vessel obstructive CHD, respectively			
Alexander et al. 2019, USA[109]	Cohort, retrospective	220	4 years		9.5%			7.7%
Sakr et al. 2019, USA[27]	Cohort, retrospective	176	1 year				14%	
Eyvazian et al. 2019, USA[32]	Cohort, retrospective	601	6 months				11%	
Rachwan et al. 2019, USA[110]	Cohort, retrospective	1011	Median time to POAF 3 days			10%		
Hu et al. 2019, Taiwan[111]	Cohort, retrospective	2081	Mean 4.29 years			1.5% in LTRs		
Dogan et al. 2019, Turkey[112]	Cohort, retrospective	30				6.7% AF, 3.3% SVT		

(Continues)

TABLE 2 (Continued)

Study (author-year, country)	Design	*N*	Follow-up duration	Cardiac events	CHD	Arrhythmia	HF	Cardiac death
Koshy et al. 2020, Australia and New Zealand[113]	Cohort, retrospective	4265	Median 7 years					5.3% (5.4 cardiac deaths per 1000 person-years)
Nejatollahi et al. 2020, Iran[114]	Cohort, prospective	120	N/A			2%		
VanWagner et al. 2020, USA[43]	Cohort, retrospective	602	Mean 43.2 months			2.8% AF		
Kwong et al. 2020, USA[16]	Cohort, prospective	1023	Median 3.44 years			13.6% AF		
Koshy et al. 2021, Australia[115]	Cohort, retrospective	319	3.6 years	23.2% at 30 days				
Cailes et al. 2021, Australia[116]	Cohort, retrospective	309	1 month	23.3%	2.5%	14.2%	6%	
Izzy et al. 2021, USA[117]	Cohort, retrospective	141	Mean 4.5 years	19.1%	9.2%	8.5%	10%	
Park et al. 2021, South Korea[118]	Cohort, retrospective	877	Median 82 months		4.1%			
So et al. 2021, Global[119]	Meta-analysis	5222	N/A			6.8% new-onset AF		

Abbreviations: ACLS, advanced cardiac life support; AF, atrial fibrillation; ALD, alcohol-associated liver disease, NASH, non-alcoholic steatohepatitis; CHD, coronary heart disease; CI, confidence interval; CVA, cerebrovascular accident; ECG, electrocardiogram; HF, heart failure; ICU, intensive care unit; IOAF, intraoperative atrial fibrillation; IQR, interquartile range; LT, liver transplant; LTR, liver transplant recipient; MI, myocardial infarction; *N*, number; N/A, not applicable; SLKT, simultaneous liver kidney transplant; SOT, solid organ transplant; UK, United Kingdom; USA, United States of America.

TABLE 3 Practice-based recommendations for risk assessment, screening, diagnosis, surveillance, prevention, and management of cardiac disease in liver transplant recipients (LTRs)[a]

a. Preventive cardiac care recommendations (applicable to all disease entities in b)	
Screening for cardiac disease–associated conditions, including diabetes mellitus, hypertension, hyperlipidemia, obesity, alcohol use, tobacco use, and renal disease, should be performed in all LTRs. (Level of evidence: 5)	
In all LTRs, lifestyle modifications should always be considered, including weight control, exercise, and cessation of alcohol use. (Level of evidence: 5)	
All LTRs should be counseled on smoking cessation. (Level of evidence: 3)	
In LTRs with CKD, consider CNI minimization strategies. (Level of evidence: 5)	
In LTRs with hypertension, nonpharmacologic therapy should include exercise, weight control, dietary salt modification and smoking cessation. (Level of evidence: 5)	
A BP target <140/<90 should be considered in all LTRs to reduce risk for cardiac events (Level of evidence: 3). A lower threshold of BP <130/80 mmHg is, however, preferred among those with multiple cardiac risk factors or those with clinical cardiac disease. (Level of evidence: 5)	
In LTRs with hypertension, selection of pharmacologic therapy should consider timing after LT, patient comorbidities and the established mechanisms of CNI-induced hypertension. For LTRs without comorbidity, it is reasonable to consider a dihydropyridine calcium channel blocker as a first line agent. (Level of evidence: 5)	
In LTRs with diabetes mellitus, HgA1c <7% should be considered, though less stringent targets could be considered in older patients or those at risk for hypoglycemia. (Level of evidence: 5)	
In LTRs with diabetes mellitus without established cardiac disease, there is insufficient evidence to recommend for or against any specific approach to management. (Level of evidence: 5)	
In LTRs with diabetes and clinical cardiac disease, SGLT2 inhibitors or GLP–1 analogues should be considered as first line anti-diabetic agents, given their cardio-protective effects in general population. (Level of evidence: 5)	
In LTRs with hyperlipidemia, lipid lowering therapy should be considered with attention to potential drug-drug interactions and expected cardiac risk reduction. LDL-C targets should be based on ASCVD risk and not absolute thresholds, as recommended in the general population. (Level of evidence: 5)	
For LTRs with overweight or obesity, weight loss is recommended with lifestyle changes and consideration of pharmacotherapy (e.g., GLP–1 analogues) or bariatric surgery, when appropriate. (Level of evidence: 5)	
b. Disease-specific recommendations	
Coronary heart disease	
Risk assessment	Risk assessment for CHD in LTRs should address early postoperative and long-term CHD risk. (Level of evidence: 5)
	Risk scores, compared with individual risk factors, may be helpful to risk stratify LTRs for CHD events. The Framingham Risk Score, Systematic Coronary Risk Evaluation Project (SCORE), and Prospective Cardiovascular Münster Study (PROCAM) models have been specifically evaluated in LTRs and may be useful in this population. Other scores have not been evaluated to date. (Level of evidence: 4)
Screening, diagnosis, and surveillance	Given the high prevalence of subclinical CHD in LTRs, it is reasonable to monitor for signs and symptoms of clinical CHD. (Level of evidence: 5)
	There is insufficient evidence to recommend for or against routine screening for subclinical CHD in asymptomatic LTRs with stress testing for assessment of ischemia or cardiac CT for the presence of CAC. (Level of evidence: 5)
Primary prevention	Consider selection of immunosuppression (e.g., tacrolimus vs. cyclosporine; mTORi; minimize steroids) to mitigate metabolic risks, when possible. (Level of evidence: 5)
	In LTRs, there is no evidence to support or refute use of aspirin 81 mg daily for primary prophylaxis against ASCVD. (Level of evidence: 5)
Management	In LTRs with clinical CHD, management of CHD-related conditions, including hypertension, hyperlipidemia, diabetes, and chronic kidney disease, and referral to subspeciality care when appropriate, should be considered for secondary prevention. (Level of evidence: 4)
	In LTRs with clinical CHD, aspirin 81 mg daily should be considered for secondary prevention. (Level of evidence: 5)
	In LTRs with clinical CHD, at least moderate intensity statin therapy is reasonable with attention to potential drug-drug interactions; high intensity statin therapy may be considered with close monitoring in LTRs who are on concurrent CNIs or mTORi. (Level of evidence: 3)
	In LTRs with clinical CHD, beta-blockers should be considered for secondary prevention. (Level of evidence: 5)

(Continues)

TABLE 3 (Continued)

Heart failure	
Risk assessment	Risk assessment for HF in LTRs should address early postoperative and long-term HF risk. (Level of evidence: 5)
Screening, diagnosis, and surveillance	Screening for HF risk factors, including cirrhotic cardiomyopathy, diabetes mellitus, hypertension, dyslipidemia, obesity, chronic kidney disease, coronary artery disease, pulmonary hypertension, valvular heart disease, or arrhythmia is warranted. (Level of evidence: 5)
	Performing focused cardiac physical exam and testing of BNP monthly for the first 3 months after transplant is reasonable in patients with pre-existing cardiac disease (e.g., CCM, coronary artery disease, pulmonary hypertension, valvular heart disease, and/or arrhythmia). (Level of evidence: 5)
	Long-term follow-up of patients with pre-existing subclinical cardiac dysfunction using comprehensive echocardiography every 6 months until resolution of systolic or diastolic dysfunction may be of benefit. (Level of evidence: 5)
Primary prevention	In LTRs with hypertension *and* asymptomatic decline in ejection fraction to <50% (i.e., without clinical manifestations of HF), anti-remodeling therapies such as beta blockers, ACE inhibitors, ARBs, ARNIs, and/or aldosterone antagonists are recommended. (Level of evidence: 5)
Management	In LTRs with HF, referral to cardiology (HF specialist, if possible) should be considered. (Level of evidence: 5)
	In LTRs with HFrEF, evidence-based guideline directed medical therapy should be applied. This includes, but is not limited to, cardiac rehabilitation, the use of beta blockers, ACE inhibitors, ARBs, ARNIs, aldosterone antagonists, GLP−1 analogues, SGLT−2 inhibitors (even in patients without diabetes), and subcutaneous defibrillators to improve mortality, functional status, and prevent future HF hospitalizations. (Level of evidence: 5)
	In LTRs with HFpEF, blood pressure control (using ACE inhibitors, ARBs, ARNIs), use of aldosterone antagonists, coronary revascularization when appropriate, and maintenance of sinus rhythm should be considered, to improve symptoms. (Level of evidence: 5)
Arrhythmia	
Risk assessment	In all LTRs, risk factors for post-LT AF should be assessed including prior history of AF, increased age (≥ 65 years), structural heart disease and diabetes mellitus. (Level of evidence: 5)
Screening, diagnosis, and surveillance	In LTRs with concern for arrhythmia, it is appropriate to obtain ECG, ambulatory rhythm monitoring, loop recorders, or potentially a pacemaker or defibrillator analysis to confirm the diagnosis. (Level of evidence: 5)
Management	In LTRs with arrhythmia, a multidisciplinary approach is recommended to guide treatment and prevent interactions with immunosuppressive medications. (Level of evidence: 5)
	In LTRs with arrhythmia, rate and rhythm control agents may be used for treatment; however, interactions with immunosuppression medications should be considered. Alternative treatments, such as direct-current cardioversion or catheter ablation, can be considered when rate and rhythm control are insufficient. (Level of evidence: 5)
	In LTRs with non-valvular AF, The CHA_2DS_2-VASc score can be used to help determine the risk of ischemic stroke to aid in decisions about anticoagulation use. (Level of evidence: 5)
	In LTRs with AF, DOACs should be considered for anticoagulation over warfarin in those patients who are eligible given non-inferior embolic risk and better safety profile. The HAS-BLED score can assess bleeding risk from anticoagulation and a multidisciplinary discussion should be considered for high-risk LTRs (HAS-BLED>3). (Level of evidence: 5)
	In LTRs with AF undergoing surgery, bridging of anti-coagulation in patients with non-valvular AF is likely only needed in patients with a very high stroke risk (CHA_2DS_2-VASc score ≥2). (Level of evidence: 5)
Valvular heart disease	
Risk assessment	History taking should include questions about symptoms potentially related to valve disease, such as exercise intolerance and presyncope. Physical examination should be performed to assess for cardiac murmurs and signs of heart failure. (Level of evidence: 5)
	New abnormal examination findings or symptoms should be evaluated with TTE. (Level of evidence: 5)
Screening, diagnosis, and surveillance	Sequential monitoring of known valvular lesions in LTRs, usually with TTE, should be performed at intervals similar to that recommended in the general population (e.g., every 1–2 years in asymptomatic patients with moderate AS and moderate mitral regurgitation). (Level of evidence: 5)
	TEE should be reserved for situations in which valve anatomy and severity of valvular dysfunction need to be clarified following TTE. In the absence of contraindications, LTRs can undergo TEE, if needed. (Level of evidence: 5)

TABLE 3 (Continued)

Primary prevention	In LTRs with prosthetic heart valves, endocarditis prophylaxis should be given prior to dental procedures, as per current guidelines. (Level of evidence: 5)
Management	In LTRs with severe AS, TAVI may be preferable to SAVR, depending on factors including patient age and comorbidities. (Level of evidence: 3)
	LTRs with other valve lesions should be managed according to current guidelines in the general population. (Level of evidence: 5)

Abbreviations: ACE, angiotensin converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; AS, aortic stenosis; ASCVD, atherosclerotic cardiovascular disease; BNP, B-type natriuretic peptide; BP, blood pressure; CAC, coronary artery calcium; CCM, cirrhotic cardiomyopathy; CHD, coronary artery disease; CKD, chronic kidney disease; CNI, calcineurin inhibitors; DM, diabetes mellitus; DOAC, direct acting anticoagulants; ECG, electrocardiogram; GLP-1, glucagon like peptide 1; HF, heart failure; HgA1C, glycated hemoglobin; LDL, low-density lipoprotein; LTR, liver transplant recipient; mTORi, mammalian target of rapamycin inhibitors; SAVR, surgical aortic valve replacement; SGLT2, sodium glucose transporter 2; TAVI, transcatheter aortic valve implantation; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

[a]Many of the above statements have strong evidence to support their validity in the general population for mitigation of cardiac disease risk, but direct evidence for the benefit or harm of such a recommendation is lacking in the liver transplant population.

dysfunction (systolic or diastolic; e.g., CCM),[30] pulmonary hypertension,[39] coronary artery disease (or regional wall motion abnormality on cardiac imaging), significant valvular disease, or arrhythmia, a cardiac-focused physical exam and a screening for elevated brain natriuretic peptide (BNP) or N-terminal pro b-type natriuretic peptide (NT-proBNP) monthly for 3 months post-LT may be of benefit. A comprehensive TTE in these patients may detect deleterious cardiac remodeling, which can prompt therapy (e.g., detecting decreased ejection fraction to <50% warrants initiation of neurohormonal blockade or other anti-remodeling therapies).[40] The optimal interval for long-term echocardiographic surveillance of high-risk LTRs or those with CCM is yet to be defined. A recent multidisciplinary, international consortium for CCM recommended echocardiographic surveillance of patients with CCM at 6, 12, and 24 months post-LT.[36] However, continued surveillance until echocardiographic resolution of cardiac dysfunction, at least in CCM patients, is reasonable, as well. Surveillance of LTRs with established HF should follow cardiology society guidelines for HF in the general population.[38]

3.2.4 | Prevention and management of post-transplant heart failure

Strategies to prevent the development of HF after LT should be tailored to the risk factors and etiology of cardiac dysfunction in LTRs. Volume overload and perhaps the risk of stress cardiomyopathy can be avoided with relatively restrictive intraoperative blood transfusion and negative fluid balance in the early postoperative period.[27,41]

Aggressive management of traditional cardiac risk factors is warranted to potentially prevent cardiac events and progression toward symptomatic HF.[42] Although hypertension is a common complication of LT affecting up to 92% of recipients, less than 30% achieved a BP of <140/90 mmHg in a recent single-center study. However, there was a 50% reduction in risk of death and a 35% reduction in the risk of cardiac events (including HF) among those with controlled BP.[43] Regarding diabetes mellitus, importantly, glucagon-like peptide 1 receptor (GLP1) agonists and sodium glucose cotransporter 2 (SGLT2) inhibitors have recently been established as cardioprotective agents with potential benefits for prevention of HF or the hospitalizations resulting from it in the general population.[44,45] In 2020, the American College of Endocrinology recommended these agents as first-line anti-diabetic agents in patients with HF and/or increased risk for atherosclerotic vascular disease given the strong supportive data.[46] Lipid control and weight management are equally important in LTRs at risk for HF.[47]

It is important to recognize the difference in the prevention strategies between HFrEF and HFpEF.[40,48] Optimal management of the aforementioned risk factors is a critical prevention strategy for both entities (HFrEF and HFpEF). Direct prevention strategies are available for HFrEF, but not for HFpEF. In asymptomatic patients with abnormally low EF (i.e., systolic dysfunction), anti-remodeling therapy may not only prevent further decline in EF and development of HF symptoms but may also improve EF in a significant proportion of patients, based on data from the general population.[48] Anti-remodeling therapies in HFrEF include angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), aldosterone antagonists, angiotensin receptor-neprilysin inhibitors (ARNI), and b-adrenergic receptor blockers (BB). ACEi, ARB, aldosterone agonists, and BB can certainly be given to patients with HFpEF with the intent of controlling blood pressure, but they do not reverse the diastolic dysfunction. Anti-remodeling therapy is also effective for secondary prevention and can improve prognosis in patients with established clinical HFrEF by decreasing hospitalizations and prolonging survival.[29,48] LTRs with established HF should be managed per guidelines for the general population with HF. Practice-based recommendations for HF management in LTRs are provided in Table 3.

3.2.5 | Knowledge gaps and future directions to mitigate post-transplant heart failure

Despite the increase in the body of literature addressing HF after LT, knowledge gaps continue to exist and warrant further investigation.

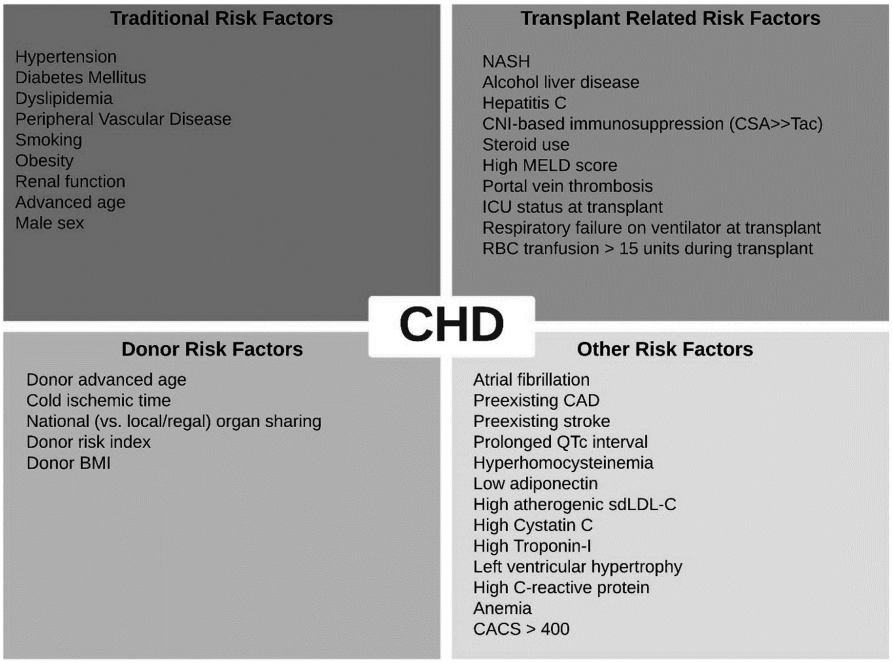

FIGURE 1 Established risk factors for coronary heart disease among liver transplant recipients. This figure demonstrates transplant recipient-specific, donor-specific, and general risk factors for coronary heart disease
CHD, coronary heart disease; BMI, body mass index; NASH, non-alcoholic steatohepatitis; CNI, calcineurin inhibitor; CSA, cyclosporine; Tac, tacrolimus; MELD, model for end stage liver disease; ICU, intensive care unit; RBC, red blood cell; LDL, low density lipoprotein; CACS, coronary artery calcium score

The prevalence of long-term HF in LTRs needs to be better defined and the utility of the primary and secondary prevention measures observed in the general population warrants validation in LTRs. The reversibility of CCM, if any, still needs to be investigated. Table 4 outlines the knowledge gaps that warrant further studies, to ultimately improve HF care in LTRs.

3.3 | Arrhythmia in liver transplant recipients

3.3.1 | Epidemiology

Cardiac arrhythmias are caused by atrioventricular conduction abnormalities (related to structural and/or functional etiologies) and are associated with adverse outcomes among LTRs, including decreased survival.[49-55] Although patients can experience atrial or ventricular arrhythmias, non-valvular atrial fibrillation (AF) is the most common arrhythmia and has the most available data in the LT setting.[56] While AF prevalence among the general population is approximately 1%–2% for those under age 65 and 9% for those over age 65,[57] both pre-LT and post-LT AF prevalence is higher ranging from 4.9 to 5.9% and 1.5 to 10%, respectively (Table 2).

3.3.2 | Risk factors for post-transplant arrhythmias

Risk factors for post-LT AF include pre-existing AF, older age, history of left ventricular hypertrophy, CHD and diabetes mellitus.[49,50,54,57,58] Non-AF arrhythmias, including ventricular arrhythmias, are much less prevalent among LTRs and thus data about risk factors are sparse.

3.3.3 | Diagnosis, screening, and surveillance for post-transplant arrhythmia

The diagnosis of cardiac arrhythmia pre- or post-LT is essential to prevent adverse post-LT outcomes. Screening electrocardiogram (ECG) is performed in all LT candidates during their transplant evaluation. A confirmatory ECG recording is needed when cardiac auscultation of heart sounds reveals an irregular rhythm and/or rapid or slow pulse in LTRs.[57] Ambulatory rhythm monitoring may be required to verify the arrhythmia diagnosis.[57] There has been no consensus on post-LT screening. However, surveillance of LTRs with a known arrhythmia should include a cardiology consultation.

3.3.4 | Prevention and management of post-transplant arrhythmia

Large-scale, RCTs evaluating efficacy and safety in the management of atrial and ventricular arrhythmias in LTRs are lacking. Guidance is often extrapolated from consensus, cardiology society-based guidelines in the general population.[59] Practice-based recommendations for the management of arrhythmia in LTRs are provided in Table 3. Unstable arrhythmias should be managed according to the universal advanced cardiovascular life support recommendations.[57,59]

Atrial fibrillation

Rate control is fundamental for all patients with AF to improve symptoms, preserve exercise tolerance, maintain quality of life, and to prevent cardiomyopathy. General consensus recommendations highlight the usage of either a BB or a non-dihydropyridine calcium channel blocker (NDCCB), depending on LVEF, as the first-line rate

TABLE 4 Research gaps in risk assessment and management of cardiac disease in liver transplant recipients

Cardiac disease type	Research gaps
Coronary heart disease	
Risk assessment	Refining what defines relevant "cardiac outcomes" in LTRs to compare findings across populations and studies
	Conducting prospective cohort studies for cardiac risk assessment and stratification
	Development and validation of risk prediction models for CHD events in post-transplant setting
Screening, diagnosis, and surveillance	Determining whether recipients of LT for NASH, hepatitis C, or alcohol-related liver disease should undergo more intensive screening or surveillance than those LTRs without these conditions
	Understanding the test performance characteristics for stress testing or cardiac CT for detection of subclinical CHD in asymptomatic LTRs
Prevention	Delineating the optimal care delivery model that reduces CHD risk in LTRs
	Investigating if certain immunosuppression strategies reduce CHD events in LTRs
	Identifying which anti-hypertensive agent(s) are most effective in reducing CHD events in LTRs
	Exploring the role of statin therapy for primary prevention of CHD events in LTRs
	Identifying an optimal algorithm for management of diabetes in LTRs that also reduces CHD events
	Determining the most effective approach to smoking cessation in LTRs
	Defining the optimal timing of pharmacotherapy and/or bariatric surgery in LTRs to reduce CHD risk
	Determining whether SGLT2 inhibitors or GLP1 analogues reduce CHD events in LTRs with clinical CHD
Management	Studying the optimal dose of aspirin therapy for secondary prevention of CHD events in LTRs
	Evaluating the safety and efficacy of high-intensity lipophilic statins in LTRs with clinical CHD
Heart failure	
Risk assessment	Prospective cohort studies are needed to evaluate the long-term prevalence of HF and its risk factors as well as impact on post-LT clinical course
	Development and validation of peri- and post-operative risk prediction models for both types of HF (with reduced ejection fraction and with preserved ejection fraction) in LTRs
	Prospective cohort studies are needed to assess the reversibility of cirrhotic cardiomyopathy post-LT
Screening, diagnosis, and surveillance	Exploring the utility of post-LT echocardiographic surveillance in patients at high risk for HF
	Identifying the optimal interval for post-LT echocardiographic surveillance in high-risk groups (e.g., patients with cirrhotic cardiomyopathy)
	Evaluating the role of biomarkers in monitoring LTRs who are at high risk for HF
Prevention	Identifying the optimal BP target to prevent HF in LTRs at high risk for HF
	Studying the use of GLP−1 analogues and/or SGLT2i for primary prevention of HF in LTRs with diabetes mellitus
	Evaluating the efficacy of anti-remodeling therapies in improving systolic dysfunction resulting from cirrhotic cardiomyopathy in LTRs
Management	Assessing the utility of cardiac rehabilitation in LTR
	Investigation of the efficacy and safety of GLP1 analogues or SGLT2 inhibitors in preventing HF readmission and death in LTRs
Arrhythmia	
Risk assessment	Prospective cohort studies are needed to evaluate the prevalence of arrhythmias (atrial or ventricular) and to risk stratify LTRs with arrhythmias
	Further development and validation of risk prediction models for cardiac arrhythmias, particularly ventricular or non-AF arrhythmias, in the post-transplant setting
Screening, diagnosis, and surveillance	Investigation of serial ECG use for pre- and post-LT patients and determining the rate at which post-LT arrhythmias are captured, potentially including machine-learning and AI algorithms
	For high-risk pre- or post-LT patients (particularly with a known arrhythmia or structural heart disease), investigating conduction studies that can improve diagnosis and surveillance
	Evaluating the use of biometric technology to help detect the presence and type of cardiac arrhythmias in LTRs

(Continues)

TABLE 4 (Continued)

Cardiac disease type	Research gaps
Prevention	Investigation into the optimal care delivery model that reduces adverse outcomes in LTRs with arrhythmias
	Evaluation of the optimal antithrombotic agent in LTRs with AF
	Delineating immunosuppression strategies or peri-operative techniques that reduce arrhythmia events in LTRs
Management	Cost-effectiveness studies to determine the efficacy of rate control versus rhythm control in LTRs with cardiac arrhythmias
	Patient selection and efficacy of ablative techniques or other EP interventions to help reduce associated outcomes compared with pharmacologic therapy in LTRs with arrhythmias
	Use of biometric monitoring to help with therapeutic response
Valvular heart disease	
Risk assessment	Case-control studies would help define and quantify risk of endocarditis associated with immunosuppression for LT
Screening, diagnosis, and surveillance	Prospective cohort studies are needed to define the prevalence of valve disease in LT candidates and LTRs and to determine how LT impacts the natural history of valve disease
Prevention	Prospective cohort studies are needed to assess whether CNI-minimization strategies reduce risk of AS development and progression
Management	Longitudinal cohort studies are needed to assess the long-term durability of TAVI in LTRs

Abbreviations: AF, atrial fibrillation; AS, aortic stenosis; BP, blood pressure; CHD, coronary heart disease; CNI, calcineurin inhibitors; CT, computed tomography; ECG, electrocardiogram; EP, electrophysiology; HF, heart failure; LT, liver transplant; LTR, liver transplant recipients; NASH, non-alcoholic steatohepatitis; SGLT2, sodium glucose cotransporter 2; TAVI, transcatheter aortic valve implantation.

control agent.[59,60] For those who are intolerant or resistant to rate control measures, antiarrhythmics, such as amiodarone, can be considered for pharmacologic rhythm control or conversion.[57,59] However, both NDCCB and antiarrhythmics must be cautiously used post-operatively as there may be interactions with calcineurin inhibitor-based immunosuppression.[54]

For symptomatic patients in whom rate or rhythm control has been ineffective and/or poorly tolerated, direct-current cardioversion (DCCV)[57] or catheter ablation may be efficacious in achieving sinus rhythm.[61] DCCV is appropriate in the setting of rapid ventricular rate, hemodynamic instability, or the presence of active myocardial ischemia or HF.[57] Whereas RCTs have confirmed the superiority of catheter ablation in maintaining sinus rhythm, as well as improving symptoms, exercise capacity, and quality of life in the general population, data for LTRs are nonexistent.[60,62]

Antithrombotic therapy for patients with AF should be tailored to each individual based on their stroke and bleeding risk.[57] The most validated stroke and bleeding risk estimation tools for AF are the CHA_2DS_2-VASc score[63] and the HAS-BLED score,[64] respectively. A major recent advance in AF-related stroke prevention is the emergence of direct oral anticoagulants (DOACs) with superior efficacy and safety and fewer drug interactions compared with warfarin.[60] However, all major RCTs of DOACs exclude patients with chronic liver disease or LTRs.[65,66] DOAC pharmacokinetics are also influenced by functional liver impairment as well as drug-drug interactions.[67] Hence, a multidisciplinary approach is needed prior to starting anticoagulation for LTRs.

When estimating the bleeding risk of anticoagulation in patients with AF, the HAS-BLED score can be used because it does include liver disease as a component.[64] In patients with non-valvular AF, most intra-cardiac thrombi aggregate in the left atrial appendage and percutaneous occlusion with the WATCHMAN device (Boston Scientific, Marlborough, MA) may be considered in patients with contraindications to long-term anticoagulation (HAS-BLED score>3).[68-71]

Ventricular arrhythmias

In patients with symptomatic premature ventricular contractions in an otherwise normal heart, treatment with a BB is useful to reduce recurrent arrhythmias and improve symptoms.[72] Treatment with an antiarrhythmics is reasonable to reduce recurrent symptomatic arrhythmias and improve symptoms if a BB and NDCCB are ineffective or not tolerated, though available agents must be thoroughly reviewed and cross-checked with immunosuppression agents. Given that patients with pre-existing ventricular arrhythmias are often not considered for LT, there is a paucity of literature evaluating the impact of ventricular arrhythmias on post-LT outcomes. However, should a post-LT ventricular arrhythmia develop, cardiology consultation would be warranted.

3.3.5 | Knowledge gaps and future directions to mitigate post-transplant arrhythmia

A growing body of literature demonstrates that AF is linked to adverse graft and patient outcomes, whereas the impact of non-AF arrhythmias on LTRs remains unclear. As LTRs become older and have more medical comorbidities, the impact of cardiac arrhythmias will likely increase over time. Thus, a better understanding of screening as well as management of arrhythmias among LTRs is essential to augment favorable outcomes. Table 4 outlines future directions

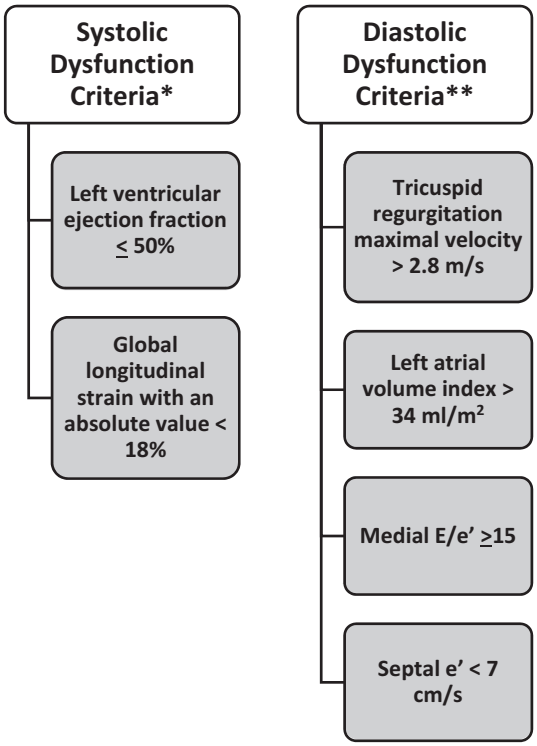

FIGURE 2 The revised criteria for cirrhotic cardiomyopathy. This figure highlights the components of comprehensive echocardiographic evaluation of systolic function and diastolic function. In the case of liver transplant candidates, systolic or diastolic dysfunction in the absence of known cardiac pathology (e.g., coronary artery disease) is diagnostic of cirrhotic cardiomyopathy. * One criterion is needed to make the diagnosis of systolic dysfunction. ** The presence of three criteria indicates the presence of advanced diastolic dysfunction that can be graded based on E/A ratio, but the presence of two criteria requires further testing to determine the degree of diastolic dysfunction

within this field that can advance our knowledge and provide long-term benefits for LTRs.

3.4 | Valvular heart disease in liver transplant recipients

3.4.1 | Epidemiology

Data on the prevalence, natural history, and outcomes of VHD among LTRs are sparse. Small studies have suggested that pre-LT mitral regurgitation, tricuspid regurgitation, and aortic regurgitation, when worse than mild, may be associated with less favorable outcomes in the immediate post-LT period and ensuing 6 months.[73,74] However, these studies did not report on mechanisms of valve regurgitation. Regurgitant lesions are often sensitive to changes in preload and afterload, and further study will be needed to determine how LT impacts outcomes in these patients. There are no published data about the risk factors for VHD after LT. The figure in Data S4 outlines the risk factors described in general population and the plausible or expected risk factors in LTRs.

3.4.2 | Diagnosis, screening, and surveillance for post-transplant valvular heart disease

No studies have specifically examined screening for VHD in LTRs. In the general population, evaluation for VHD is most often triggered by symptoms of HF, abnormal physical examination findings such as murmurs, and/or screening of asymptomatic patients in specific situations such as family history of bicuspid aortic valve and personal history of rheumatic fever. Similar principles should be followed in LTRs.

The initial diagnostic test for VHD is almost always TTE. Sequential monitoring of known valvular lesions in LTRs, usually with TTE, should be performed at intervals similar to those recommended in the general population (e.g., every 1–2 years in asymptomatic patients with moderate aortic stenosis [AS] or moderate mitral regurgitation), as per current guidelines.[75] In patients with concomitant CKD, calcific valve lesions—most notably, AS—can progress more rapidly, and more frequent TTEs might be advisable.[76]

With regard to other imaging modalities, transesophageal echocardiography (TEE) is usually reserved for situations in which valve anatomy and severity of valvular dysfunction need to be clarified following TTE. As in the general population, calcium scoring by non-contrast computed tomography can help clarify AS severity, particularly among patients with suspected low-flow, low-gradient AS. cMRI can be useful for quantifying regurgitant lesions, especially aortic and mitral regurgitation, and for assessing myocardial pathology.[76]

3.4.3 | Management of post-transplant valvular heart disease

The bulk of the literature on valve disease in LTRs focuses on management of AS. However, prospective, and longitudinal studies are still lacking. A recent report by Elbadawi et al.[77] used the nationwide inpatient sample (NIS), a claim-based database, to evaluate outcomes of transcatheter aortic valve implantation TAVI versus surgical aortic valve replacement SAVR among 1,730 hospitalizations in solid organ transplant recipients from 2012 to 2017; 24% ($n = 410$) were LTRs. Over the study period, TAVI became more common than SAVR among transplant recipients. Factors associated with TAVI versus SAVR were age >65 years, diabetes, and prior coronary artery bypass grafting. A propensity-matched analysis accounting for organ type, clinical characteristics, and hospital teaching status showed that in-hospital mortality, post-operative bleeding, requirement for blood transfusion, acute kidney injury, vascular complications, acute stroke, median length of stay (3 vs. 8 days), and discharge to nursing facility were all significantly less likely with TAVI compared with SAVR. This cross-sectional analysis showed that TAVI was safe and better tolerated with fewer complications compared with SAVR. A similar analysis using the NIS from 2012 to 2015[78] compared TAVI outcomes among LTRs, kidney transplant (KT) recipients, and patients with no history of transplant. A total of 62,399 TAVI patients were identified: 62,180 (99.6%) with no history of transplant, 219 (0.4%) with KT, and 85 (0.1%) with LT. No significant differences

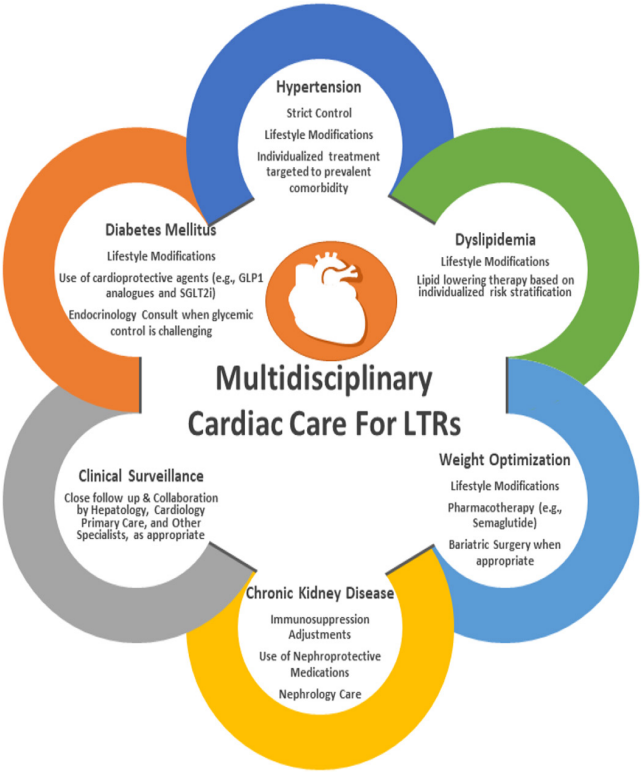

FIGURE 3 The elements of multidisciplinary care for liver transplant recipients with established cardiac disease. This figure summarizes the necessary measures that should be followed to optimize outcomes in liver transplant recipients with cardiac disease. These measures surround metabolic syndrome, chronic kidney disease, and surveillance of cardiac disease

were noted in in-hospital mortality or major cardiovascular, respiratory, or neurological complications among the groups, although the sample size of LTRs was modest. Practice-based recommendations for management of VHD in LTRs are provided in Table 3.

3.4.4 | Knowledge gaps and future directions to mitigate post-transplant valvular heart disease

Further research is needed to define the prevalence of valve disease in LT candidates and LTRs and to determine how LT impacts the natural history of valve disease (Table 4). As a result of immunosuppression, LTRs may be at greater risk of infective endocarditis than the general population,[79] although the magnitude of risk is unclear.

4 | IMMUNOSUPPRESSION AND CARDIAC DISEASE IN LIVER TRANSPLANT RECIPIENTS

Mounting data support a potential role for the use of mTORi-based immunosuppression to benefit the CV risk profile of solid organ transplant recipients. CNI minimization and renal sparing regimens (e.g., everolimus-based regimen) may potentially ameliorate the risk for cardiac events through improvement in renal function,[80] which has been supported in KT recipients in findings from the ELEVATE trial.[81] However, whether switching to mTORi therapy has direct cardioprotective effects is unclear in LTRs as there are no targeted studies in this population. Moreover, despite the fact that a switch to mTORi in cardiac transplant recipients has been associated with LV mass reduction,[82,83] in KTRs, early conversion to everolimus showed no effect on LV mass in both the ELEVATE and CENTRAL trials.[81,84] These two trials also showed mixed results in terms of whether a switch to mTORi from CNI improves blood pressure. Some studies suggest an improvement in arterial stiffness with mTORi use[85,86]; however, this was not true in ELEVATE.[81] There may also be some immunomodulatory benefits to mTORi use based on studies in heart transplant recipients where mTORis may reduce arteriosclerosis,[87,88] though there are no similar data in LTRs. Finally, mTORi use is associated with attenuated weight gain compared with CNI use which may also have an impact on CV risk.[89] The potential benefits of mTORi also need to be balanced against the known effects of mTOR inhibition on lipid profiles, proteinuria and new onset diabetes.

5 | CONCLUSION

With the increased burden of cardiac disease among LTRs, optimizing cardiac care becomes critical. Figure 3 delineates the essential elements needed for this care optimization in LTRs. The advancement in the knowledge about cardiac disease in LTRs and the rapid evolution of diagnostic, preventive, and therapeutic modalities for cardiac disease in the general population indicate the need for a clinical practice guidance tailored to LTRs and their unique cardiometabolic risk profile. The multidisciplinary practice-based recommendations outlined in this article provide comprehensive clinical guidance surrounding cardiac disease evaluation and management after LT and identify knowledge gaps that can pave the path for future investigations in this field. Specifically, long-term interventional studies are needed to validate the data extrapolated from the general population regarding primary and secondary prevention of cardiac disease in LTRs. Such studies can guide future refinement of these recommendations in the years to come.

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SUPPORTING INFORMATION

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