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# Understanding and managing cardiovascular outcomes in liver transplant recipients

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## Abstract

**Purpose of review—**Cardiovascular disease (CVD) is a common cause of mortality after liver transplantation. The transplant community is focused on improving long-term survival. Understanding the prevalence of CVD in liver transplant recipients, precipitating factors as well as prevention and management strategies is essential to achieving this goal.

**Recent findings—**CVD is the leading cause of death within the first year after transplant. Arrhythmia and heart failure are the most often cardiovascular morbidities in the first year after transplant which could be related to pretransplant diastolic dysfunction. Pretransplant diastolic dysfunction is reflective of presence of cirrhotic cardiomyopathy which is not as harmless as it was thought. Multiple cardiovascular risk prediction models have become available to aid management in liver transplant recipients.

**Summary—**A comprehensive prevention and treatment strategy is critical to minimize cardiovascular morbidity and mortality after liver transplant. Weight management and metabolic syndrome control are cornerstones to any prevention and management strategy. Bariatric surgery is an underutilized tool in liver transplant recipients. Awareness of ‘metabolic-friendly’ immunosuppressive regimens should be sought. Strict adherence to the cardiology and endocrine society guidelines with regard to managing metabolic derangements post liver transplantation is instrumental for CVD prevention until transplant specific recommendations can be made.

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**Keywords**

coronary artery disease; dysrhythmia; heart failure; liver transplant; metabolic syndrome

## INTRODUCTION

After undergoing a life-saving liver transplantation, the major challenge will be prolonging a good quality life for the recipients. This challenge is largely attributed to the high incidence of life-threatening conditions in this patient population. Hepatic disease, malignancy, and cardiovascular disease (CVD) have been shown to be the most common causes of death after the first year of liver transplant with CVD affecting more than 10% of liver transplant recipients (LTR) [1]. These observations date back to a previous era and it is plausible that with the advent of more optimized immunosuppression (ISP) regimens, antiviral agents, and organ preservation techniques, hepatic causes of death may not be as prominent, leaving cardiovascular diseases, and malignancy the leading causes of death in LTRs. Although the incidence of de novo malignancy could be potentially ameliorated by adaptation of lower levels of ISP and stricter screening protocols [2], curbing cardiovascular diseases and the risk factors post-transplant remains challenging. Many risk factors pre-exist transplantation, particularly as nonalcoholic steatohepatitis (NASH)-related cirrhosis with concomitant metabolic syndrome begins to dominate the transplant community [3■]. Risk factors either worsen or evolve after transplant such as ISP-related effects on metabolic syndrome or its components [4]. More recently, data showed the unfavorable impact of CVD is not exclusively limited to long-term post-transplant course but affects early post-transplant outcomes as well. In a large national cohort, the main causes of death within the first month post liver transplant were CVD (42.1%) followed by infection (27.9%) and graft failure (12.2%) [5]. Aside from CVD-related mortality, the incidence of CVD as a comorbid illness post liver transplant was also found to be significantly high. A recent meta-analysis showed that the incidence of cardiovascular events is approximately 22% in the first 6-month post liver transplantation and 12% after 6-month post liver transplantation [6]. These data suggest that more study is needed to better predict cardiovascular events, improve diagnostic testing, and optimize management options in this special population.

## CARDIOVASCULAR RISK FACTORS POST LIVER TRANSPLANTATION

Metabolic syndrome is highly prevalent in LTRs affecting approximately half of this patient population [7]. Albeldawi *et al.* evaluated 775 LTRs and noted higher cardiovascular events (61.4 and 34.1% at 1 and 3 years) in those with post-transplant metabolic syndrome compared with patients without post-transplant metabolic syndrome (4.5 and 10% at 1 and 3 years) [8]. The relation between various immunosuppressive medications and the components of metabolic syndrome is illustrated in Table 1.

The underlying liver disease is another factor that has an impact on post-transplant outcomes. Patients with underlying NASH were found to have higher incidence of early (i.e., 1st year) post liver transplantation cardiovascular events compared with those with underlying alcohol-related liver disease (26 vs. 8%) [9]. Another comorbidity that has an

established association with CVD is chronic kidney disease, which is common after LTRs given the use of calcineurin inhibitors (CNIs). Davis and colleagues have shown that pretransplant renal failure is an independent factor for post liver transplantation CVD (hazard ratio 2.1) and reduced cardiac event-free survival (hazard ratio 2.2) [10]. These findings were complemented in another study that showed that cardiovascular mortality after 1-year post liver transplantation is significantly associated with post liver transplantation kidney disease [1].

## CORONARY ARTERY DISEASE POST LIVER TRANSPLANTATION

Coronary artery disease (CAD) is traditionally the most investigated subtype of CVD given the magnitude of its consequences on patient outcomes especially mortality. A long-term follow-up of LTRs showed that CAD with or without myocardial infarction constituted 39.8% of the cardiovascular events encountered within nearly a decade post liver transplant. It is noteworthy that the study showed that the incidence of cardiovascular events was 15% at 3 years and 30% at 8-year post liver transplantation. Interestingly, the same study showed that pretransplant troponin I elevation (>0.07 ng/ml) is associated with post-transplant de novo CVD [11]. Another study showed elevation of troponin I (≥0.1 ng/ml) early post-transplant is associated with higher 30-day mortality post-transplant [12]. These observations may indicate subtle (i.e., subclinical or microvascular) CAD that was not evident on the widely used pretransplant stress testing. To this end, a recent study showed that significant CAD requiring revascularization comprises 12% of the cardiovascular complications in the first year after transplant [13■■]. These studies raise the concern about inadequacy of pre-liver transplantation stress testing and the need for more frequent use of coronary catheterization in this high-risk populations. A recent meta-analysis evaluated the utility of dobutamine stress echocardiographic testing (DSE) and myocardial perfusion scintigraphy (MPS) in predicting CAD diagnosed using the gold standard coronary catheterization in liver transplant candidates. It revealed that the pooled sensitivity was 28% and 61% and specificity was 82% and 74% for DSE and MPS, respectively. It is notable that the risk factors that prompted coronary catheterization in most of the studies analyzed in this meta-analysis were not identified which can certainly impact the observed sensitivity [14]. It has been proposed that liver transplant candidates with multiple conventional CAD risk factors need to undergo coronary catheterization. NASH has emerged as an independent risk factor for CAD and should be counted for while risk stratifying these patients for DSE vs. cardiac catheterization [9]. With the outstanding data regarding coronary computed tomography (CT) accuracy in identifying CAD [15], coronary CT can become the more reliable (compared with DSE and MPS) less invasive (compared with cardiac catheterization) modality in our patient population; however, the available data to date about its use in LTRs are scarce [16].

## HEART FAILURE POST LIVER TRANSPLANTATION

Heart failure after transplantation may be relatively common, depending on how it is defined. More than 2 decades ago, it was noted that during the first postoperative week chest radiographs showed pulmonary edema or vascular congestion in up to half the patients [17]. Numerous studies since then have demonstrated the presence of at least transient heart

failure in 7–43% of patients in the early to late postoperative period [18-22,23■■,24]. It is possible that such heart failure is part of the spectrum of cirrhotic cardiomyopathy (CCM) manifesting after transplantation, although this remains speculative [25]. Cirrhotic cardiomyopathy represents cardiac dysfunction (systolic or diastolic) in the absence of previously known heart disease in patients with end stage liver disease and is thought to be due to myocardial fibrosis, myocardial hypertrophy, and subendocardial edema [26■,27■]. Heart failure can be divided into two types. The first is heart failure with reduced ejection fraction (HFrEF) which corresponds to systolic heart failure [28]. The second is heart failure with preserved ejection fraction (HFpEF) which generally corresponds to diastolic dysfunction or failure [28,29].

All studies to date on heart failure in the posttransplant period have been retrospective. Moreover, widely variable criteria for systolic dysfunction, diastolic dysfunction, and CCM have been used in the studies which makes it very difficult to draw definitive conclusions at this time. However, despite the limitation some preliminary conclusions can be tentatively drawn. One study reported that pretransplant diastolic dysfunction was associated with increased graft rejection and failure [22], but other studies [19,23■■] did not find such an association. Preliver transplantation diastolic dysfunction was associated with post-transplant mortality in two studies [19,22]. Furthermore, pre-liver transplantation diastolic dysfunction has been found to be an independent predictor of post liver transplantation systolic heart failure [19,23■■]. HfpEF or diastolic dysfunction appears to be more prevalent post-transplant than HFrEF. Rates of diastolic dysfunction are reported to be 3–43% [18-21,23■■,24]. This large scatter is due to the different definitions of diastolic dysfunction: most studies used some of the newer criteria from the echocardiographic consensus guidelines of the American Society of Echocardiography (ASE) and European Association of Cardiac Imaging (EACI) [30], whereas a few still used the 2005 Montreal CCM definition which is now thought to be outmoded. In contrast, the variability in reported prevalence of HFrEF in the post-transplant period is much lower, 2–7% [18,20,21,23■■,24]. The lower scatter reflects that the vast majority of patients have normal ejection fraction more than 55% as those with HFrEF prior to transplant are not listed for transplant due to poor cardiac reserve.

Given the potential unfavorable impact of preliver transplantation diastolic dysfunction on post liver transplantation outcomes, it is important to implement the diastolic dysfunction echocardiographic parameters outlined in the ASE/EACI guidelines from 2015 in the echocardiographic evaluation of liver transplant candidates [30]. Closer cardiovascular monitoring of those patients is important given risk of progression into clinical heart failure.

To better understand CCM and cardiac dysfunction in general in LTRs, large multicenter prospective studies are needed, using standardized diagnostic criteria. Finally, more mechanistic translational research in animal models and therapeutic trials in patients are necessary to advance the field.

## DYSRHYTHMIA POST LIVER TRANSPLANTATION

The most common abnormality encountered on ECG in liver transplantation candidates and recipients is a prolonged QT interval, defined as a rate-corrected QT interval (QTc) greater than 0.45 s for males and 0.47 s for females [26■]. The risk of sudden cardiac death (SCD) increases when QTc is more than 0.5 s [29]. Despite its commonality, the clinical implication of a prolonged QTc in cirrhosis is not well understood [26■]. Noteworthy is that in the majority of cases, the QT interval normalizes following liver transplantation [26■]. There is, however, an increase in post liver transplantation cardiac events and mortality when QT prolongation is present [20,32]. Given the association of prolonged QTc with ventricular arrhythmia, the presence of a prolonged QTc on ECG following liver transplantation should prompt further investigation of associated causes, including medications known to prolong the QT interval. A patient history of unexplained syncope or a family history of SCD in conjunction with a prolonged QTc should prompt referral to a cardiology consultant for further assessment possible congenital long-QT syndrome and consideration of implantable defibrillator or other therapy [31,33-35].

Atrial fibrillation is the most commonly encountered tachyarrhythmia. The prevalence of preexisting atrial fibrillation among liver transplantation candidates ranges from 1.4 to 6% [36,37]. Atrial fibrillation is associated with an elevated incidence of adverse intraoperative and postoperative cardiovascular complications, and a trend towards graft dysfunction and mortality [36-38]. Nearly 50% of early (i.e., <1 year) complications after liver transplantation include heart failure and arrhythmias, such as atrial fibrillation [5,36]. A high prevalence of pretransplant CCM, which is characterized by subclinical myocardial dysfunction in patients with end-stage liver disease, is likely a primary contributing factor to this observation [26■]. Another risk factor for atrial fibrillation that is common in the post liver transplantation setting is hypertension [39], often attributed to worsening metabolic profile post liver transplantation mainly due to ISP.

## CARDIOVASCULAR RISK PREDICTION IN THE LIVER TRANSPLANT RECIPIENT

Risk assessment is a critical step in the approach to primary and secondary prevention of cardiovascular complications in LTRs. As previously noted, cardiovascular complications are a leading cause of both short-term and long-term morbidity and mortality in liver transplant recipients [5,35,36]. It’s important to recognize that most published guidelines for cardiovascular risk prediction focus primarily on risk for atherosclerotic CVD (ASCVD). However, studies in liver transplantation recipients demonstrate that risk for ASCVD is a late complication (>1-year post liver transplantation) related to ongoing exposure to traditional cardiovascular risk factors including hyperlipidemia, diabetes, hypertension, and renal disease that may develop and/or worsen in the setting of chronic ISP use after transplantation [11]. Conversely, as outlined above, CVD in the early post-transplant period (<1 year) mostly consists of heart failure and arrhythmia. Thus, when thinking about risk prediction for cardiovascular complications in the liver transplantation recipient it is important to consider the timeframe from liver transplantation. Recently, a novel risk

prediction score, called Cardiovascular Risk in Orthotopic Liver Transplantation (CAROLT), was proposed to predict cardiovascular events in the first-year post liver transplantation using a group of pre-liver transplantation demographic, social, and clinical variables. It is available online (https://carolt.cbits.northwestern.edu) [13■■].

In the United States, the most commonly used quantitative ASCVD risk scores include the Framingham General CVD Risk Score (FRS) [40], the Pooled Cohort Equations (PCEs) [41], and the Reynolds Risk Score [42]. The PCEs-ASCVD score is the one recommended by the American College of Cardiology for guiding statin initiation-related decisions and it is available online (https://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/). In European cohorts, the Prospective Cardiovascular Münster Study (PROCAM) [43] and Systematic Coronary Risk Evaluation Project (SCORE) [44] have also been evaluated for predicting ASCVD risk.

Among liver transplantation recipients, the FRS has moderate discrimination for coronary events (*c*-statistic 0.70), but tends to underestimate risk overall [45]. In a single small study of liver transplantation recipients published over 15 years ago, PROCAM and SCORE had somewhat improved discrimination (*c*-statistics 0.78 and 0.80, respectively), however the study was significantly limited by a low coronary event rate among which these scores were tested and by the fact that 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors (i.e., statins), which significantly alter cardiovascular risk profiles, were not used in the population studied [46]. Guidelines from the American Heart Association (AHA) and the American College of Cardiology (ACC) recommend use of the PCEs to assess both 10-year and lifetime ASCVD risk [47,48]. However, patients with cirrhosis and LTRs were not included in the studies used to derive these equations and thus, the predictive ability of the PCEs in our patient population is unknown. Similarly the discrimination and calibration of the Reynolds Risk Score has not been studied in liver transplantation recipients.

Other important factors to consider in prediction of quantitative ASCVD risk in liver transplantation recipients is cardiovascular risk factor duration. Recently, investigators demonstrated that the long-term risk of major cardiovascular events is greatest in liver transplantation recipients with sustained post-transplantation diabetes mellitus, with a 13% and 27% cumulative incidence of a major cardiovascular event at 5 and 10 years, respectively [49■■]. Finally, heart failure, in particular HFpEF, is an important cardiovascular complication not captured by the aforementioned scores. However, to date there are no well-validated scoring systems for heart failure prediction either in the general population nor specifically in patients with cirrhosis or after liver transplantation.

In summary, the PCE-ASCVD score can be used for long-term cardiovascular risk prediction in LTRs until data become available about long-term risk prediction model that is specific to this patient population and is inclusive of all entities of CVD. For short-term post liver transplantation cardiovascular risk prediction (i.e., within first year after transplant), CAROLT may be used.

## MANAGEMENT AND RISK REDUCTION

After the remarkable improvement in post-transplant care with regard to preserving graft function via improved ISP and infection prophylaxis protocols, LTRs are expected to live longer. This advancement in post-transplant care comes with a price which is developing comorbid medical illnesses during this prolonged life time. As mentioned above, the post-transplant course is often notable for weight gain, impaired glucose tolerance, hypertension, and dyslipidemia. These metabolic derangements can be attributed to immunosuppressive medications [4,50]. Weight loss is an effective tool that targets the components of metabolic syndrome [51]. In addition to routine exercise and following healthy diet regimen, immunosuppressive regimen can have a role in weight management. Everolimus combination with reduced tacrolimus dosing was found be associated with a small reduction in weight gain 2 years after transplant compared with regular dose of tacrolimus monotherapy. Interestingly, the study showed that the rates of metabolic syndrome were comparable in these two groups [52■]. With regard to CVD risk, CNIs were found to be associated with lower CVD risk compared with other types of ISP in one study [53] while Sirolimus (mammalian target of rapamycin inhibitor, mTORi) was found to be cardioprotective in another study [54]. Although intuitively one may assume mTORi may lower CVD risk, a recent study comparing CNIs with Sirolimus was unable to prove a difference between the two groups [55].

Surgical weight loss has proven effective in improving other components of metabolic syndrome as well as CVD and related mortality [56,57]. A recent report of long-term outcomes of bariatric surgery in general population showed durable weight loss as well as remission or prevention of type 2 diabetes, hypertension, and dyslipidemia 12 years later [58■]. This could be especially important in obese LTRs as the continuous potential for weight gain can limit the success and durability of medical means for weight loss. Simultaneous sleeve gastrectomy with liver transplant has shown durable weight reduction with favorable effects on hypertension and diabetes [59■■]. Reports of post-transplant bariatric surgery have also shown promising results with regard to amount of weight loss and absence of negative impact on graft or ISP [60-62]. Despite these results and despite the American Association for the Study of Liver Diseases (AASLD) recommendation to consider bariatric surgery for post liver transplantation morbid or severe obesity [63], the hesitation continues in many bariatric centers about performing this surgery in this patient population due to concerns about surgical risks.

Although statin use has a proven benefit in preventing or ameliorating CVD, this class of medication is likely under-utilized in LTRs. In 2013, AASLD recommended adopting LDL cut off of 100mg/dl for initiation of therapeutic interventions [63]. Since the conventional lipid profile testing might not accurately reflect the atherogenic status and cardiovascular risk of the patient, using ASCVD risk stratification tool was deemed more appropriate for CVD prevention. In 2016, the United States Preventive Services Task Force recommended initiating low to moderate-dose statins in patients between 40 and 75 years old without history of CVD who have one or more CVD risk factors (dyslipidemia, diabetes, hypertension, or smoking) and a calculated 10-year CVD event risk of at least 10%. Prior data have already shown that cardiovascular event risk in LTRs exceeds 10% [1]. The task

force also recommended ‘selective’ offering of low to moderate-dose statins to patients 40–75 years without history of CVD who have one or more CVD risk factors and a calculated 10-year CVD event risk of 7.5–10% [64]. Given the increased risk of CVD in LTRs, it will be reasonable to include them in this selective offering of therapy. Another component of metabolic syndrome and risk for cardiovascular events is hypertriglyceridemia for which the AASLD 2013 guidelines recommended using Omega 3 fatty acids as first line therapy and fibrates as second line therapy. Patients on the latter regimen should be closely monitored for side effects especially when they are concurrently on statin or CNIs. The most recent guidelines by American Association of Clinical Endocrinologists in 2017 also recommended these agents for treatment of hypertriglyceridemia more than 500mg/dl [65]. In a recent study, fish oil was associated with improved post liver transplantation survival in a cohort that was transplanted for NASH [66].

Given the prevalence of diastolic dysfunction (as a component of CCM) pre-liver transplantation which might not be reversible post liver transplantation [26■,67], identifying these patients pre-liver transplantation (using the aforementioned recent ASE guidelines) and maintaining strict control of blood pressure can help preventing progression into more advanced stages of heart failure (i.e., clinical heart failure) [68]. Better control of hypertension can also minimize the possibility of cardiac arrhythmia as well as myocardial ischemia [69]. The most recent ACC/AHA guidelines recommend 130/80 as the cut off for blood pressure control [70]. In LTRs, Amlodipine is typically the preferred anti-hypertension agent except in patients with proteinuria, diabetes, or chronic kidney disease where angiotensin converting enzyme inhibitor or angiotensin receptor blocker would be preferred [63].

Lastly, achieving glycemic control is essential in cardiovascular prevention [71]. Therefore, monitoring for development of post-transplant diabetes mellitus (PTDM), even after discontinuation of steroids, is critical. Once PTDM is diagnosed, the treatment approach should be per the most recent guidelines by American Diabetes Association (ADA, 2018 guidelines) where metformin is the first line therapy in patients with glycated hemoglobin (A1c) less than 9% and where dual therapy with another oral agent or insulin can be considered at higher A1c levels. Glucose-like peptide 1 analogues may be considered upon adding agents to metformin given their proven impact on weight reduction and cardiovascular risk reduction [72]. There have been no major safety concerns about use of Diabetes therapeutic agents in LTRs [73]. It is important to note that these ADA guidelines also recommend considering initiation of metformin in patients with prediabetes (A1c 5.7–6.4%) especially for those with BMI at least 35 $kg/m^2$ or younger than 60 year-old [72]. To this end, a prior large cohort showed that glycemic control relation with CVD and mortality is linear even for A1c below the diagnostic cut off for diabetes [71] which implies that CVD risk exists in patients with prediabetes as well. This highlights the importance of checking A1c level, perhaps annually, in nondiabetic LTRs.

## CONCLUSION

CVD is common after liver transplant and is one of the leading causes of short-term and long-term mortality in LTRs. With the advances in post-transplant care, LTRs will continue

to live longer and be at higher collective risk of CVD. Therefore, improved pre-liver transplantation CAD diagnosis strategies, better preliver transplantation recognition of heart failure risk by CCM identification, and aggressive post liver transplantation preventive strategies are needed (Table 2).

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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**KEY POINTS**

- CVD is a leading cause of mortality in the early and late post-transplant course.
- Cirrhotic cardiomyopathy may not be reversible and may lead to post-transplant heart failure.
- Post-transplant weight loss via surgical and medical means can be instrumental in decreasing risk for cardiovascular disease.
- Adherence to society guidelines with regards to managing dyslipidemia, hypertension, and diabetes mellitus is critical for cardiovascular disease prevention.

**Table 1.**

Immunosuppressive drugs and metabolic profile

| Immunosuppressive agents | Hyperlipidemia | Hypertension | Obesity | Diabetes |
|---|---|---|---|---|
| Calcineurin inhibitors | +<br>Cyclosporine > Tacrolimus | ++<br>Cyclosporine > Tacrolimus | + | ++<br>Tacrolimus > Cyclosporine |
| Antiproliferative agents<br>Azathioprine<br>Mycophenolate mofetil | No effect | No effect | No effect | No effect |
| Steroids | + | ++ | + | +++ |
| Mammalian target of rapamycin inhibitor | +++ | + | – | + |

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**Table 2.**

Risk factors and prevention of cardiovascular disease in liver transplant recipients

| Risk factors | CV sequela post-LT | Risk prevention/management |
|---|---|---|
| Pretransplant CAD | CAD | Cardiac catheterization of high-risk liver transplant candidates<br>Consideration of potentially more reliable, less invasive coronary screening tools (compared to stress testing) such as coronary CT |
| Diabetes mellitus | CAD<br>Heart failure | Early detection and treatment including that of prediabetes |
| Hypertension | CAD<br>Heart failure<br>Atrial fibrillation | Adopting the new blood pressure goal of <130/80 |
| Dyslipidemia | CAD | Treating patients with statin according to the ASCVD risk estimation<br>Treating hypertriglyceridemia of >500 mg/dl |
| Weight gain | CAD<br>Hypertension<br>Diabetes mellitus | Lifestyle modifications<br>Bariatric surgery<br>Everolimus-based immunosuppression<br>GLP-1 analogues in diabetic patients |
| Diastolic dysfunction (cirrhotic cardiomyopathy) | Heart failure<br>Atrial fibrillation | Pre-LT identification<br>Strict blood pressure control |

ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CT, computed tomography, CV, cardiovascular; GLP-1, glucose like peptide-1; LT, liver transplantation.