Special Article

Preoperative cardiovascular investigations in liver transplant candidate: An update

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ABSTRACT

Cardiovascular complications are a major cause of morbidity and mortality in patients with end-stage liver disease (ESLD) undergoing liver transplantation. Identifying candidates at the highest risk of postoperative cardiovascular complications is the cornerstone for optimizing the outcome. Ischaemic heart disease contributes to major portion of cardiovascular complications and therefore warrants evaluation in the preoperative period. Patients of ESLD usually demonstrate increased cardiac output, compromised ventricular response to stress, low systemic vascular resistance and occasionally bradycardia. Despite various recommendations for preoperative evaluation of cardiovascular disease in liver transplant candidates, a considerable controversy on screening methodology persists. This review critically focuses on the rapidly expanding body of evidence for diagnosis and risk stratification of cardiovascular disorder in liver transplant candidates.

Key words: Cardiovascular system evaluation, liver transplant, preoperative evaluation

INTRODUCTION

Over last three decades, liver transplantation (LT) has emerged as the definitive treatment for patients with decompensated end-stage liver disease (ESLD). Improved surgical techniques along with better perioperative management and advances in postoperative immunosuppression have transformed LT from being a high-risk and high-mortality procedure to a routinely performed surgery.[1,2] The candidates for LT usually have multiple comorbidities including cardiovascular disease.[3] Presence of cardiovascular disease is a predictor of poor prognosis within this patient population.[1] Hence, the identification of those at risk remains a key clinical priority and requires a systematic and exhaustive pretransplantation cardiovascular assessment.

The authors searched articles published on liver transplant between 1990 and December 2013 on PubMed with keywords: Liver transplant, preoperative evaluation, preoperative cardiovascular evaluation and preoperative cardiac evaluation. The full text articles published in English language were considered. The relevant references cited in the bibliography of selected articles were also retrieved. The authors reviewed the available literature to analyse the association between preoperative cardiovascular evaluation techniques and postoperative outcomes.

Cardiovascular disease consequent to porto-pulmonary hypertension and hepato-pulmonary syndrome were not included.

SPECTRUM OF CARDIOVASCULAR DISEASES IN PATIENTS FOR LIVER TRANSPLANT

The cardiovascular involvement in ESLD patients may vary from subtle electrocardiogram (ECG) changes to heart failure [Table 1]. The presence of high resting cardiac output (CO) and low systemic vascular resistance (SVR) in ESLD and perioperative haemodynamic alterations during LT adversely affect the outcome of patients with cardiovascular involvement.[4]

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CORONARY ARTERY DISEASE

The overall prevalence of coronary artery disease (CAD) in chronic liver disease (CLD) has been reported to be 2–28% with highest prevalence in patients aged over 50 years.[5,6] In liver disease, chronic inflammation and decreased SVR along with increased blood flow can predispose to plaque rupture and thus, precipitate the acute coronary syndrome. Furthermore, increased metabolic demand may worsen these adverse conditions. The degree of coronary artery stenosis does not always determine the symptomatology of CAD.[7]

Risk factors for CAD are also prevalent in liver transplant candidates.[8] Age >50 years, male gender, hypertension, altered lipid metabolism, diabetes mellitus and obesity are the most prevalent clinical attributes. The presence of two or more factors (other than age) places these patients at a moderate to severe risk of CAD.[8] Further, the diagnosis of nonalcoholic steatohepatitis (NASH) independently increases the risk of CAD with critical CAD occurring in approximately 23% of patients.[9]

Despite the advances in diagnosis and management of CAD and improved perioperative techniques of LT, the mortality and morbidity rates still remain significantly high.[1,2] Hence, identification of asymptomatic patients with critical CAD continues to be a big challenge.

Table 1: Spectrum of cardiovascular involvement in ESLD

Prolonged QTc on ECG
Hypertension
Ischemic heart disease
Cardiomyopathy
Systolic dysfunction
Diastolic dysfunction
Heart failure
Hepato-pulmonary syndrome
Porto-pulmonary hypertension

QTc – Corrected QT; ESLD – End-stage liver disease; ECG – electrocardiogram

CARDIOMYOPATHY

Alcohol abuse can potentially damage both liver and the heart. Heart failure may occur even before the occurrence of significant liver damage.[10] The spectrum of cardiac involvement in heavy drinkers varies from diastolic abnormality of left ventricle with or without ventricular hypertrophy, alcoholic nonischaemic dilated cardiomyopathy involving both ventricles to cirrhosis associated cardiomyopathy.[11] The latter is characterised by impaired contractile responsiveness to stress or altered diastolic function with electrophysiological abnormalities without any other known cardiac disease.[12] The cardiac manifestations of cirrhosis can occur regardless of the aetiology of cirrhosis.[13] However, no significant difference has been reported in cardiac structural and functional parameters between alcoholic and nonalcoholic cirrhosis.[14] The features of cirrhotic cardiomyopathy are summarized in Table 2.[15]

Systolic dysfunction

Systolic dysfunction in cirrhotics is characterized by inability of heart to increase ejection fraction under stress.[16] Systolic dysfunction also explains the high incidence of pulmonary oedema (18%) in cirrhotics after LT.[13]

Diastolic dysfunction

The trans-mitral blood flow is altered in about half of patients with cirrhosis.[17] Diastolic dysfunction is more severe in patients with ascites and usually precedes systolic dysfunction.[18] It may result in pulmonary oedema and heart failure following orthotopic liver transplantation (OLT) and transjugular intrahepatic portosystemic shunt (TIPSS) and thus contributes to high morbidity and mortality.[19]

Electrophysiological abnormality

Prolonged corrected QT (QTc) interval is present in 45% of cirrhotics.[16] Prolongation of the QTc may lead to electromechanical uncoupling. This may lead to

Table 2: Diagnostic criteria for cirrhotic cardiomyopathy

Systolic dysfunction	Diastolic dysfunction	Supportive criteria
Blunted increase in cardiac output with stress (exercise, volumes and pharmacological)	E/A ratio <1.0 (age-corrected)	Electrophysiological abnormalities
	Prolonged deceleration time (>200 ms)	Abnormal chronotropic response
Resting ejection fraction <55%	Prolonged isovolumetric relaxation time (>80 ms)	Electromechanical uncoupling
		Prolonged QTc interval
		Enlarged left atrium
		Increased myocardial mass
		Increased cardiac enzyme and biomarker

QTc – Corrected QT, E/A Ratio: early to late ventricular filling velocity rato

sudden cardiac death in cirrhotics following stressful condition like OLT and TIPSS.[16] Mohamed *et al*. found higher incidence of prolonged QTc in patients who died after LT than the survivors.[20] On long term, OLT often improves or normalizes QTc prolongation in 50% of the patient population.[21]

Autonomic dysfunction

The majority (87%) of patients who undergo LT suffer from autonomic dysfunction.[22] Four years mortality is 30% in patients of ESLD with dysautonomia compared to 6% without dysautonomia.[23] The degree of dysautonomia usually improves after LT in up to 63% of patients within 6–7 months.[22]

HYPERTENSION

Chronic alcohol intake may contribute to blood pressure elevation.[11] In addition, Kadayifci *et al*. observed prevalence of hypertension significantly higher in patients with NASH related cirrhosis.[24] However, due to decreased SVR in ESLD, most patients do not require pretransplant treatment for hypertension.[25]

CARDIAC EVALUATION IN LIVER TRANSPLANTATION CANDIDATE

It is recommended to evaluate a LT candidate for any active cardiac condition by completing a detailed history and physical examination (Class I). Generally, routine preoperative cardiovascular tests are performed in the form of ECG and two-dimensional echocardiography [Table 3]. Further investigations are done as per the individual characteristics and transplant center protocols. Studies of clinical importance that have evaluated various modalities for preoperative cardiac assessment in LT recipients have been summarized in Table 4. Currently, there is scarcity of guidelines that outline the optimal cardiovascular risk stratification strategy for LT candidates. This is perhaps because there is still a significant knowledge gap in the study of cardiovascular outcomes.

Electrocardiography

A 12-lead ECG is part of routine cardiac evaluation in liver transplant candidate. Prolonged QTc interval is the common ECG abnormality in patients with CLD.[16]

Two-dimensional echocardiography

Echocardiography is helpful in detecting structural and functional heart abnormalities.[36] Right ventricular systolic pressure or pulmonary artery pressure can also be measured with Doppler echocardiography. The presence of hepatopulmonary syndrome may also be evaluated by echocardiography with bubble contrast.[37]

Stress testing

High prevalence of CAD, inability of CLD patients to perform exercise and significant cardiovascular instability during LT necessitates pharmacological stress testing before LT. However, literature provides controversial evidence in terms of both the optimum stress imaging modality in this patient group and its utility in predicting outcomes.[38]

DOBUTAMINE STRESS ECHOCARDIOGRAPHY

Dobutamine stress echocardiography (DSE) is the most widely used screening tool for risk stratification. The clinical effect of dobutamine mimics haemodynamic conditions encountered during LT. The sensitivity and specificity of DSE in patients of CLD vary from 12–100% to 57–100% respectively.[39] This appears secondary to the inability to reach target heart rate possibly due to chronotropic incompetency and beta blocker therapy. In a retrospective analysis, Harinstein *et al*. observed sensitivity, specificity and negative predictive value (NPV) of DSE to be 13%, 85% and 75% respectively in CAD with obstruction >70%. The authors concluded that coronary angiography (CAG) should be performed in liver transplant recipients who are at high-risk for CAD.[32] Williams *et al*. concluded that DSE positivity did not correlate with intraoperative cardiac events.[40] Safadi *et al*. examined the correlation between preoperative DSE and adverse cardiac events at 30 days and concluded that an abnormal stress echocardiography was not associated with adverse cardiac outcome but normal stress test had a very high NPV (>90%) in all patients undergoing LT.[31]

NUCLEAR MYOCARDIAL PERFUSION SCANNING

Dipyridamole or adenosine also demonstrate conflicting results as chronic vasodilatory state in CLD limits the drug induced vasodilation and necessary increase in coronary blood flow. In an observational analysis, Bradley *et al*. reported approximately 93% patients have a low-risk myocardial perfusion imaging (MPI), 5% have an intermediate-risk MPI, and 2% have a high-risk MPI study. They concluded that stress MPI results should not be considered for determining cardiac risk and eligibility for LT.[29] In a single-photon emission computed tomography (SPECT) imaging study

Table 3: Cardiovascular evaluation for liver transplant

Initial screening	Advanced		
	Noninvasive	Stress testing	Invasive
12-Lead ECG	Calcium scoring	Stress echocardiography	Trans-esophageal echocardiography
Resting echocardiography	Cardiac magnetic resonance	Stress thallium	Coronary angiography
		Contrast echocardiography	
		Cardio pulmonary exercise testing	
		6-min walk test	

ECG – Electrocardiography

Table 4: Studies that report evaluation for cardiovascular disease in liver transplant patients

Author, year	Nature of study	Number of patients evaluated	Method of evaluation	Result of the study
Jodocy *et al.* 2012[26]	Observational	54	CTA and CCS	44% presented with CCS above 300 and/or a significant stenosis. CTA combined with CCS is a useful non-invasive imaging technique for pre-LT assessment of coronary artery disease
Chae *et al.* 2012[27]	Prospective observational	247	CTCAG	CTCAG test should be included in the routine pre-transplant cardiac workup
Prentis *et al.* 2012[28]	Prospective	Total 182 transplanted 60	CPET	Preoperative cardiorespiratory reserve (as defined by CPET) a sensitive and specific predictor of early survival after liver transplantation
Bradley *et al.* 2010[29]	Retrospective	763	MPI	Low risk in 710 patients (93%), intermediate risk in 36 patients (5%), and high risk in 17 patients (2%)
Aydinalp *et al.* 2009[30]	Prospective	93	MPI (93) coronary angiography 93	Abnormal MPI 68.8%,(sensitivity 90%, specificity 61%) severe CAD 9.4% on CAG
Safadi *et al.* 2009[31]	Retrospective	403	DSE	Normal DSE 93.8%, abnormal DSE 6.2% NPV >90%
Harinstein *et al.* 2008[32]	Retrospective	Total105, primary study group 64	DSE and CAG	DSE had a low sensitivity (13%), high specificity (85%), low PPV (22%) and intermediate NPV (75%) for obstructive CAD
McAvoy *et al.* 2008[33]	Prospective observational	101	CAC score	Moderate CAC in 37.6% of patients, with 19.8% classified in a high-risk group
Tiukinhoy-Laing *et al.* 2006[8]	Retrospective cohort analysis	161	Right and left cardiac catheterization	Severe CAD 20%, moderate CAD 26%, mild CAD 36%, no CAD 18%
Zoghbi *et al.* 2003[34]	Retrospective	339	SPECT imaging (87) coronary angiography (34)	Abnormal SPECT 8%, minimal CAD 88%, moderate CAD 6%, severe CAD 6% on CAG
Davidson *et al.* 2002[35]	Retrospective	83	SPECT imaging (83) Coronary angiography (83)	MPS had a sensitivity of 37% and specificity of 63% to detect significant (>70%) coronary lesions. 23% had positive CAG
Donovan *et al.* 1996[5]	Prospective	190	DSE (165) 2D ECHO (190) Coronary angiography (18)	DSE: Normal wall motion/no ischemia 89.7%, Induced ischemia in 7%, Resting wall motion abnormality but no inducible ischemia in 4%. 33.3% patients with ischemic DSE had significant CAD on CAG. 11.1% patients with non-ischemic DSE had significant CAD on CAG

CTA – Computed tomographic angiography; CCS – Coronary calcium scoring; LT – Liver transplant; CTCAG – Computed tomographic coronary angiography; CPET – Cardiopulmonary exercise testing; MPI – Myocardial perfusion imaging; CAD – Coronary artery disease; PPV – Positive predictive value; NPV – Negative predictive value; CAG – Coronary angiography; DSE – Dobutamine stress echo-cardiography; CAC – Coronary artery calcium; MPS – Myocardial perfusion scintigraphy; SPECT – Single-photon emission computed tomography

where all perfusion abnormalities were accepted as positive, sensitivity and specificity was 37%, and 63% respectively in severe CAD (stenosis >70%).[35] In a prospective study, Aydinalp *et al.* found the specificity and sensitivity of myocardial perfusion scintigraphy (MPS) to be 61% and 90% in severe CAD (stenosis >70%). Results of myocardial perfusion scanning were abnormal in 68.8% and normal in 31.2%. Of patients with abnormal scans, only 9.4% had severe CAD when CAG was done in patients with abnormal MPS results.[30]

Thus, noninvasive stress testing may help in identifying patients who are at very low-risk for poor cardiac outcomes.

REAL-TIME STRESS MYOCARDIAL CONTRAST PERFUSION ECHOCARDIOGRAPHY

Several studies have shown that real-time stress myocardial contrast perfusion echocardiography (RTMCE) increases the sensitivity and accuracy of DSE in detection of angiographically significant

CAD.[41] Tsutsui *et al.* studied wall motion and myocardial perfusion in 230 patients with RTMCE. Eighty five of these patients underwent LT. They found that 2 years mortality was 24% among patients with normal myocardial perfusion scanning and 45% among those with abnormality.[42] This preliminary observation points toward the increased value of this new imaging technique but further studies are warranted to assess the value in stratifying cardiovascular-risk.

CARDIOPULMONARY EXERCISE TESTING

Cardiopulmonary exercise testing (CPET) simultaneously evaluates the cardiovascular and respiratory system during exercise. Epstein *et al.* found that markers of cardiovascular reserve, peak oxygen consumption (VO_2) and oxygen consumption at anaerobic threshold (VO_2-AT), are associated with 100 days outcome following hepatic surgery, whereas resting cardiac and pulmonary function are not.[43] Prentis *et al.* concluded that submaximal CPET predicts 90 days survival after LT.[28] Though, CPET may provide interesting information, its role in evaluation of LT candidates requires further investigation.

6-MIN WALK TEST

6-min walk test (6MWT) has been found to be significantly lower in ESLD patients than in healthy adults.[44] In a prospective study, Carey *et al*. observed that 6MWT was inversely related to model for end-stage liver disease score and pretransplant 6MWT < 250 m was associated with risk of death on wait list.[45] In another study, Beyer *et al.* observed improvement in 6MWT post-LT.[46] 6MWT has not been compared to more established modes of investigations and prediction of posttransplant outcomes. Hence, it is of limited value.

CORONARY CALCIUM SCORING

Coronary artery calcium using cardiac computed tomography is an accurate tool to identify early atherosclerotic disease in asymptomatic individuals.[47,48] Calcium score (Agatston Score) directly correlates with the risk of CAD.[48] In an observational study including 54 patients, Jodocy *et al.* found that 44% presented with coronary calcium scoring (CCS) above 300 and/or a significant stenosis. Remaining 56% patients with normal computed tomographic angiography (CTA) findings were listed for LT without further tests. None of the 54 patients developed cardiovascular events perioperatively. The authors indicated that CTA combined with CCS is a useful noninvasive imaging technique for pre-LT assessment of CAD.[26] Nonetheless, the usefulness of CAC in predicting perioperative and postoperative cardiovascular events in patients undergoing OLT requires further prospective evaluation.

CARDIAC MAGNETIC RESONANCE IMAGING

The clinical applications of Cardiac Magnetic Resonance Imaging (CMR) include assessment of ventricular function, myocardial viability, myocardial perfusion, cardiomyopathy, valvular and other structural heart disease. A prospective trial by Greenwood *et al.* demonstrated that stress CMR has high diagnostic accuracy in detecting significant CAD and is superior to nuclear stress testing.[49] In the setting of disease affecting both heart and liver like haemochromatosis, CMR may be useful to certain the severity of iron load. Studies are required to establish the role of CMR in the pretransplant evaluation.

CORONARY ANGIOGRAPHY

Coronary angiography is performed to evaluate the presence of CAD in patients with known CAD, more than one cardiovascular-risk factor (other than age) and a positive stress test. According to the American College of Cardiology and the American Heart Association, performing routine CAG in this patient population carries more risk than benefit (class III recommendation).[50] High incidence of clotting disorders and renal insufficiency in the LT candidates may theoretically result in more procedural complications. However, the complications of angiography can be minimized by correcting the coagulopathy before the procedure and by adopting a transradial approach.[51]

Computed tomographic CAG (CTCAG) is emerging as a new modality in noninvasive assessment of CAD and now being used as a useful alternative to CAG. But there is only limited data available for its utility in preoperative evaluation of liver transplant patients.[52] Chae *et al.* assessed the clinical value of CTCAG and concluded that CTCAG test should be included in the routine pretransplant cardiac workup, along with thallium SPECT.[27]

SUMMARY

A systematic and algorithmic approach to evaluate preoperative cardiac risk in LT candidates may be helpful to optimize post-LT outcome. The same used at

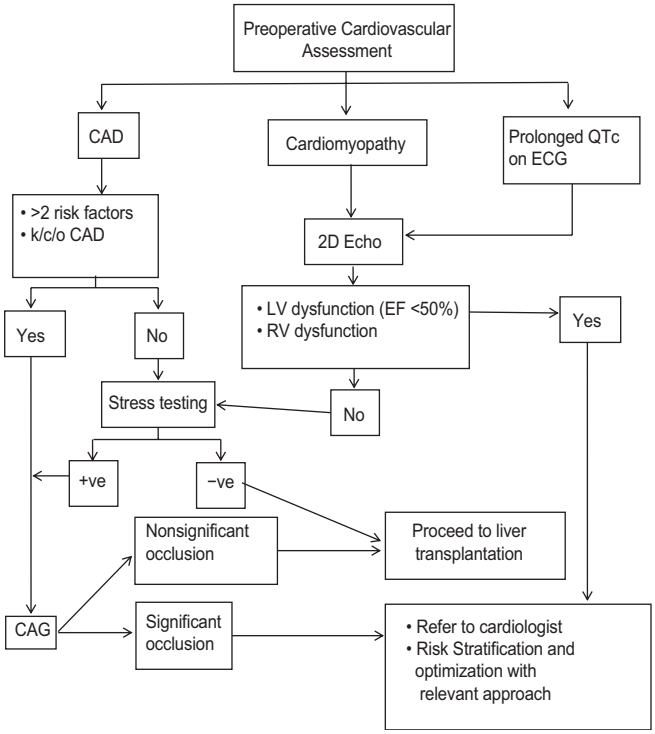

Figure 1: Algorithmic approach towards preoperative cardiovascular evaluation of liver transplant candidates. ECG – electrocardiogram; CAD – Coronary artery disease; LV – Left ventricle; RV – Right ventricle; EF – Ejection fraction

authors' respective institutions is depicted in Figure 1. Furthermore a large multi-centric study to compare different modalities for preoperative cardiac evaluation may help in elucidating best approach to patients with occult or overt cardiac dysfunction.

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