Original Article

Prevalence of myocardial perfusion abnormalities in end-stage liver disease

Ahmed Fathala, Bander Safar, Ahmed Al Muhaideb

Cardiovascular Imaging and Nuclear Medicine, Department of Medical Imaging Service, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

ABSTRACT

Background: The prevalence of coronary artery disease (CAD) in end-stage liver disease (ESLD) being evaluated for orthotopic liver transplantation (OLT) is unclear based on variable definition used for CAD. **Objective:** The aim of this study to investigate the prevalence of abnormal stress myocardial perfusion single-photon emission computed tomography (MPS) imaging, as a marker for CAD, among patients with ESLD who were referred for stress MPS imaging as a routine work up before OLT. **Materials and Methods:** This was a single-center, retrospective study. We reviewed data on 167 patients who were referred for MPS as a routine work up before OLT over the last 2 years. All patients underwent evaluation for CAD risk factors [age, hypercholesterolemia, diabetes mellitus (DM), hypertension (HTN), and smoking], and stress MPS as per standard protocol. **Results:** The total number of patients referred for stress MPS was 167. Seven patients (4% of total study population) were excluded from the study due to poor and/or nondiagnostic studies. 147 patients (92%) had normal, but only 13 patients (8%) had abnormal MPS scans. DM and male gender were the most independent risk factors for abnormal MPS with *P* value of 0.046, and 0.26, respectively. There was no significant association between the abnormal MPS result and HTN, hypercholesterolemia, smoking, age or etiology of the liver disease. **Conclusion:** Based on our data, the prevalence of abnormal MPS and left ventricular ejection fraction in patients with ESLD was found to be 8%. DM and male gender were the most independent predictor factors for abnormal MPS. True prevalence of CAD and usefulness of MPS in patients with ESLD can only be studied using a very large and randomized prospective study.

Keywords: End stage liver disease, myocardial perfusion SPECT, coronary artery disease

INTRODUCTION

Cardiovascular disease is a major cause of morbidity and mortality and accounts for up to 70% of the major adverse clinical advents in the first year following liver transplantation. Indeed, cardiovascular disease remains the leading cause of non–graft-related death in the longer term.[1] Although the high incidence of cardiovascular events post-transplant is regarded as being multifactorial, the increased prevalence of components of the metabolic syndrome (abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance ± glucose intolerance, proinflmatory state, and prothrombotic state) attributed to the immunosuppressant therapy post-transplant, is important.[2] The exact prevalence of coronary artery disease (CAD) in patients with end-stage liver disease (ESLD) being evaluated for orthotopic liver transplantation (OLT) is unclear based on the available definition and diagnostic methods used for diagnosing CAD in this population.[3] The assessment of CAD with coronary angiography (CA) in patients who were being evaluated for OLT revealed that among those who had no prior history of ischemic heart disease and were currently asymptomatic, 13.3% had coronary stenosis greater than 70%.[4] However, based on data from other studies utilizing CA as a diagnostic technique for CAD diagnosis, the prevalence rate ranged from 2.9 to 24.5%.[5-9] Given a 2.5% prevalence rate of CAD in the asymptomatic men in the general population, the former belief that CAD is uncommon in patients with ESLD no longer appears to be true.

Experience with stress myocardial perfusion single-photon emission computed tomography (MPS) in patients with ESLD is limited and conflicting. The usefulness of MPS perfusion imaging

Access this article online

Quick Response Code:

Website: www.ijnm.in

DOI: 10.4103/0972-3919.84588

Address for correspondence:
Dr. Ahmed Fathala, Department of Medical Imaging Service, King Faisal Specialist Hospital, P.O. Box 3354, MBC: 28, Riyadh, Saudi Arabia.
E-mail: ahm35799@hotmail.com

in ESLD has been demonstrated in some studies. A normal stress MPS study identified patients at a very low risk for early and late cardiac events despite a high risk profile. Furthermore, the prevalence of abnormal MPS in this study was 9%.[10] In contrary, Davidson *et al.* found a very limited role of MPS testing in cardiac risk assessment before liver transplantation because only 13% of patients who underwent preoperative MPS testing had positive scans, which reflects a low prevalence of CAD in this population. Furthermore, only one of those (1.5%) had a high-risk scan. Similarly, only one patient with known CAD had a reduced left ventricular ejection fraction (LVEF). Subsequently, the author please see above change from investigator to name of the author concluded that routine MPS testing "to rule out cardiomyopathy" does not appear justified in asymptomatic (from a cardiac standpoint) patients with ESLD. No major cardiac perioperative events (death or myocardial infarction) were noted in the study population.[11] Also, some investigators found a limited role for noninvasive stress MPS testing in cardiac risk assessment before liver transplantation and demonstrated that stress MPS imaging has a poor predictive value for CAD in OLT candidates.[12]

The aim of this study was to determine the prevalence of abnormal MPS as a marker of CAD and abnormal LVEF as marker of cardiomypathy or heart failure in all patients with ESLD undergoing assessment for OLT. The long-term goal will be to correlate these findings with cardiovascular events postoperatively.

MATERIALS AND METHODS

Patient population

This was a retrospective study that had been approved by institutional review board. One hundred sixty-seven consecutive patients with end-stage liver who are being considered for OLT were enrolled in this study. All the patients had undergone stress MPS as a routine work up. The electronic and paper charts of each patient were reviewed, and baseline demographics, medical history, and etiology of ESLD were recorded. Patients with known CAD, unstable medial conditions or nondiagnostic stress MPS studies were excluded.

Table 1: Clinical characteristic of the study population

Total	*n*=160
Gender (male/female)	108/52
Age (years)	
Normal MPS	57±7
Abnormal MPS	61±10
Clinical risk factors	
Diabetes*	65 (41%)
Hypertension**	54 (39%)
Hypercholesterolemia$	40 (25%)
Smoking	29 (18%)

MPS: myocardial perfusion single-photon emission computed tomography; *Defined as fasting blood sugar more than 126 dl (7 mmol/l) or treatment with insulin and or oral hypoglycemic drugs; **Defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≤90 mmHg and/or the use of antihypertensive medication; $Defined as serum total cholesterol ≥230 mg/d (6.2 mmol/l) or treatment with lipid lowering drugs

Preoperative myocardial perfusion single-photon emission computed tomography imaging

In our institution, preoperative MPS imaging is performed as a routine investigation in all transplant candidates who have two or more CAD risk factors such as DM, HTN, hypercholesterolemia, or symptoms suggestive of CAD. MPS with technetium-99m sestamibi or technetium-99m myoview imaging was performed according to the standard recent guidelines of American Society of Nuclear Cardiology (ASNC).[13] Stress testing was done with dipyridamole in 137 patients and treadmill exercise in 23 patients. All patients had ECG gated SPECT imaging. A single reader performed the image interpretation. Abnormal SPECT imaging results were defined as reversible (ischemia) or fixed (scar) perfusion defects (or both) and quantified as small, moderate, or large. Abnormal stress SPECT was classified as low risk (perfusion defect less than 10% of the myocardium), moderate risk (perfusion defect in the range of 10–20% of the myocardium) and high risk (perfusion defect more than 20% of the myocardium) and abnormal ejection fraction (EF) of less than 35%. LVEF was calculated on gated images; LVEF less than 50% was considered abnormal.

Statistical analysis

Categorical data are presented as percent frequencies and compared between groups by chi-square or Fisher's exact test. Continuous variables are presented as mean ± 1 SD. Student's *t* test was used to determine differences between continuous variables. Type I error was set at 5%. A *P* value equal to or less than 0.05 was considered statistically significant.

RESULTS

Patients' characteristics

The pertinent demographic data of the study patient population are shown in Table 1. Only 7 patients out of 167 were excluded for one or more of the following reasons. The MPS study was not diagnostic in three patients due to one or more of the following excessive extracardiac activity motion artifacts or Left bundle branch block (LBBB) and false-positive result could not be excluded; and three patients refused to have stress test and/or stress imaging [Figure 1]. Thirteen patients out of total 160 had abnormal stress SPECT that corresponds to 8% of the estimated prevalence. The number of low-, moderate-, and high-risk scans was 7, 2, 4, respectively. The mean EF was 61±9%. Twelve (7.5%) out of 160 patients who completed rest and gated stress imaging had low LVEF (less than 50%).

Association between abnormal stress myocardial perfusion single-photon emission computed tomography and coronary artery disease risk factors

CAD risk factors were as follows: DM 65 (41%), HTN 54 (39%), hypercholesterolemia 40 (25%), smoking 29 (18%), male gender, and age more than 55 years. There was a strong correlation between abnormal MPS and DM (*P*=0.46) and male gender (0.26), but there was no association with HTN (*P*=1), hypercholesterolemia (*P*=0.849), age (*P*=0.047), smoking

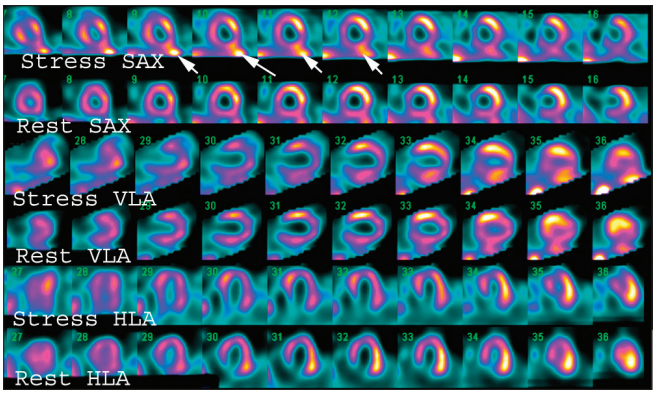

Figure 1: Nondiagnostic myocardial perfusion SPECT in a 59-year-old male who was a liver transplant candidate. Stress images shows extensive extracardiac activity adjacent to the inferior wall of the left ventricle (arrows), a common finding in patients with liver disease due to ascites and bowel activity. The rest of the images show normal myocardial perfusion. To role out coronary artery disease, coronary computed tomography was performed, and showed normal coronary arteries (SAX: short axis, VLA: vertical long axis, HLA: horizontal long axis)

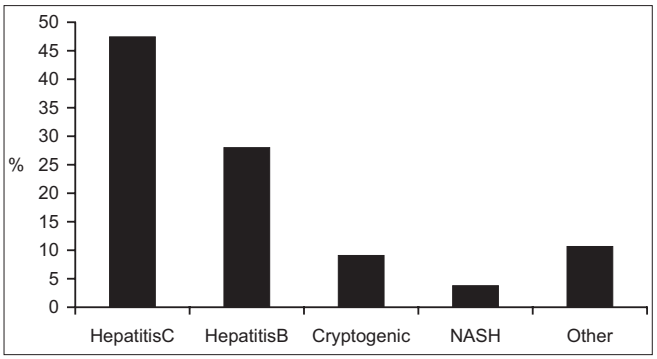

Figure 2: The etiology of end-stage liver disease that is being considered for liver transplantation. Others indicate autoimmune hepatitis, Wilson disease, alcoholic liver disease, and schistosomiasis

(*P*=0.62) or etiology of the liver disease (*P*=0.79). In multivariate analysis, the only significant correlation was observed with male gender (odds ratio 7).

In our patient population, the etiology of ESLD was as follows: Hepatitis C (HC) 75 (47%), Hepatitis B (hep B) 45 (28%), cryptogenic 15 (9%), nonalcoholic steatohepatitisNASH 7 (4%) and others (include primary sclerosing cholangitis, autoimmune hepatitis, Wilson disease, schistosomiasis, and alcoholic liver disease) 18 (11%) [Figure 2]. The etiology of the liver disease had no correlation with result of stress MPS imaging.

DISCUSSION

The main conclusion of this study is that the prevalence of abnormal stress MPS in patients with ESLD who are being evaluated for OLT is low (only 8%). Furthermore, the prevalence of high-risk stress SPECT is very low; only 4 patients (2.5%) had abnormally high-risk scan out of 160. The prevalence of abnormal EF (less than 50%) is 7.5%. In addition, there is a significant association between abnormal EF and abnormal MPS, suggesting that the etiology of cardiomyopathy in ESLD is most likely to be CAD. Both DM and male gender are the most independent predictive factors for abnormal MPS.

Prevalence of coronary artery disease in end-stage liver disease

The exact prevalence of CAD in patients with ESLD is extremely variable based on current literature. Our data suggest that 8% of these patients had abnormal stress MPS. Unfortunately, the prevalence of abnormal SPECT in our general population is unknown for comparison. However, our data are concordant with those of the previous studies of Zoghbi *et al.*[10] and Kryzhanovski *et al.*[11] Zoghbi *et al.* demonstrated that the MPS studies were normal in 91% of patients despite the high-risk profile of these patients compared with those with no MPS studies, and most importantly, they found that patients with normal perfusion and left ventricular function had a low cardiac event rate during the 2-year post-transplant period. Kryzhanovski *et al.*[11] found that the prevalence of abnormal MPS study in ESLD was 13%. Only 1.5% had high-risk scan, and 7.9% and 3% had low- and intermediate-risk scan, respectively.

Unfortunately, the sensitivity and specificity of MPS in patients with ESLD have been reported to be very low in previous studies. Davidson *et al.*[12] found the sensitivity and specificity of MPS in patients with ESLD and compared the MPS with CA and found that the sensitivity and specificity are 37% and 63%, respectively. This is very low compared to the sensitivity and specificity of stress MPS in the general population, which have been reported to be 83–90% and 82–92%, respectively.[14,15] The poor sensitivity of stress MPS in patients with ESLD has been postulated to some factors that include decreased arterial vascular resistance and impaired typical response of the coronary arteries to vasodilator agents. Other noninvasive cardiac imaging techniques such as Dobutamine stress echocardiography DSE may be more sensitive but less specific for screening CAD in this population. It has been shown that the sensitivity and specificity of DSE in ESLD is 75% and 57%, respectively, although only 18 patients were studied.[8] Some authors have suggested that the true prevalence of the occurrence, nature, and clinical implication of CAD in patients with ESLD can only be studied using a very large and randomly selected groups of patients with different etiologies of liver disease and cirrhosis, who undergo a detailed cardiovascular assessment including MPS, rest and stress echocardiography, and CA.[16] This evaluation must include the presence or absence of CAD risk factors and other possible factors that are common with this population such as anemia, pulmonary condition and nutritional and metabolic derangements.[11]

Prevalence of cardiomypathy in patients with end-stage liver disease

Our data show that the prevalence of abnormal systolic dysfunction in this population is 7.5% (12 out of 160 patients) having a strong correlation with abnormal stress MPS. This finding suggests that the etiology of cardiomypathy in ESLD is most likely related to CAD. It has been thought that the prevalence of cardiomyopathy is greater in patients with ESLD

than in the general population.[17,18] Patients with ESLD have multiple problems that place them at a risk of heart failure. Patients with liver disease have defects in both systolic and diastolic function which only become obvious with physiologic stress such as liver transplantation. In addition to CAD, there are some factors that may contribute to cardiomyopathy in ESLD. The collective pathologic changes that occur in patients with ESLD are termed as "cirrhotic cardiomyopathy" and occur to some degree in all patients with liver disease.[19] Although the clinical presentation of the cirrhotic cardiomyopathy can be variable, all patients have four common features. These are: (1) baseline increased cardiac output; (2) attenuated systolic contraction and diastolic relaxation; (3) electrophysiological abnormalities including repolarization change; and (4) a reduced response of the heart to direct beta stimulation (β-incompetence). These changes occur in the absence of overt congestive failure.[20]

Relationship between coronary risk factors and abnormal myocardial perfusion single-photon emission computed tomography result

In our population, DM (P=0.046) and male gender (P=0.26) were the most predictive risk factors for the SPECT result, but there was no association between MPS result and HTN, hypercholesterolemia, etiology of ESL, or age. Our results are very similar to those of Cary *et al.*[4] who showed that diabetes was the most predictive risk factor, and those without risk factors do not require extensive preoperative cardiac evaluation. Impaired fasting glucose is a surrogate marker of hepatic insulin resistance. Moderate or severe insulin resistance was found in one study to be 77.2% in patients with ESLD, presumably a reflection of ESLD. Insulin resistance is important in the pathogenesis of the metabolic syndrome, and a correlation between components of the metabolic syndrome and the coronary artery calcification, which is a surrogate for coronary artery atherosclerosis, was found.[21]

Study limitations

There are several limitations to our study. It was a retrospective and nonrandomized patient population study. There was no correlation with CA which is currently the gold standard for assessment of CAD; subsequently, this prevalence was based on MPS result only. Nevertheless, our results seem to be similar to those of other previous studies. In addition, perioperative complications such as myocardial ischemia, myocardial infarction, or heart failure and postoperative follow-up are not available.

CONCLUSION

Based on our data, the estimated prevalence of abnormal MPS and LVEF in patients with ESLD is found to be approximately 8%. The most independent risk factors for CAD in these patients are DM and male gender. There is no association between MPS and CAD risk factors such as HTN, hypercholesterolemia, or smoking history. Currently, there are still limited data regarding the prevalence of CAD in ESLD and usefulness of MPS in these patients. A large, randomized, prospective study is highly recommended to assess the true prevalence of CAD and usefulness of MPS in patients with ESLD.

REFERENCES

1. Pruthi J, Medkiff KA, Esrason KT, Donovan JA, Yoshida EM, Erb SR, *et al.* Analysis of causes of death in liver transplant recipients who survived more than 3 years. Liver Transpl 2001;7:811-5.
2. Rabkin JM, Corless CL, Rosen HR, Olyaei AJ. Immunosuppression impact on long-term cardiovascular complications after liver transplantation. Am J Surg 2002;183:595-9.
3. Keeffe BG, Valantine H, Keeffe EB. Detection and treatment of coronary artery disease in liver transplant candidates. Liver Transpl 2001;7:755-61.
4. Carey WD, Dumot JA, Pimentel RR, Barnes DS, Hobbs RE, Henderson JM, *et al.* The prevalence of coronary artery disease in liver transplant candidates over age 50. Transplantation 1995;59:859-64.
5. Fili D, Vizzini G, Biondo D, Pietrosi G, Volpes R, Palazzo U, *et al.* Clinical burden of screening asymptomatic patients for coronary artery disease prior to liver transplantation. Am J Transplant 2009;9:1151-7.
6. Tiukinhoy-Laing SD, Rossi JS, Bayram M, De Luca L, Gafoor S, Blei A, *et al.* Cardiac hemodynamic and coronary angiographic characteristics of patients being evaluated for liver transplantation. Am J Cardiol 2006 15;98:178-81.
7. Plotkin JS, Benitez RM, Kuo PC, Njoku MJ, Ridge LA, Lim JW, *et al.* Dobutamine stress echocardiography for preoperative cardiac risk stratification in patients undergoing orthotopic liver transplantation. Liver Transpl Surg 1998;4:253-7.
8. Donovan CL, Marcovitz PA, Punch JD, Bach DS, Brown KA, Lucey MR, *et al.* Two-dimensional and dobutamine stress echocardiography in the preoperative assessment of patients with end-stage liver disease prior to orthotopic liver transplantation. Transplantation 1996;61:1180-8.
9. Blei AT, Mazhar S, Davidson CJ, Flamm SL, Abecassis M, Gheorghiade M. Hemodynamic evaluation before liver transplantation: Insights into the portal hypertensive syndrome. Clin Gastroenterol 2007;41 Suppl 3:S323-9.
10. Zoghbi GJ, Patel AD, Ershadi RE, Heo J, Bynon JS, Iskandrian AE. Usefulness of preoperative stress perfusion imaging in predicting prognosis after liver transplantation. Am J Cardiol 2003;92:1066-71.
11. Kryzhanovski VA, Beller GA. Usefulness of preoperative noninvasive radionuclide testing for detecting coronary artery disease in candidates for liver transplantation. Am J Cardiol 1997;79:986-8.
12. Davidson CJ, Gheorghiade M, Flaherty JD, Elliot MD, Reddy SP, Wang NC, *et al.* Predictive value of stress myocardial perfusion imaging in liver transplant candidates. Am J Cardiol 2002;89:359-60.
13. Holly TA, Abbott BG, Al-Mallah M, Calnon DA, Cohen MC, DiFilippo FP, *et al.* Single photon-emission computed tomography. Nucl Cardiol 2010;17:941-73.
14. Loong CY, Anagnostopoulos C. Diagnosis of coronary artery disease by radionuclide myocardial perfusion imaging. Heart 2004;90 Suppl 5:V2-9.
15. Fleischmann KE, Hunink MG, Kuntz KM, Douglas PS. Exercise echocardiography or exercise SPECT imaging? A meta-analysis of diagnostic test performance. JAMA 1998;280:913-20.
16. Jain D. Cardiovascular involvement in patients with liver cirrhosis. J Hepatol 2005;42:3-4.
17. Nagarakanti R, Whellan D, Rubin S, Mather PJ. Reversible cardiomyopathies. Cardiol Rev 2007;15:178-83.
18. Torregrosa M, Aguade S, Dos L, Segura R, Gonzalez A, Evangelista A, *et al.* Cardiac alterations in cirrhosis: Reversibility after liver transplantation. J Hepatol 2005;42:68-74.
19. Mandell MS, Tsou MY. Cardiovascular dysfunction in patients with end-stage liver disease. J Chin Med Assoc 2008;71:331-5.
20. Wong F, Girgrah N, Graba J, Allidina Y, Liu P, Blendis L, *et al.* The cardiac response to exercise in cirrhosis. Gut 2001;49:268-75.
21. McAvoy NC, Kochar N, McKillop G, Newby DE, Hayes PC. Prevalence of coronary artery calcification in patients undergoing assessment for orthotopic liver transplantation. Liver Transpl 2008;14:1725-31.

How to cite this article: Fathala A, Safar B, Al Muhaideb A. Prevalence of myocardial perfusion abnormalities in end-stage liver disease. Indian J Nucl Med 2011;26:7-10.

Source of Support: Nil. **Conflict of Interest:** None declared.