CASE REPORT

Utility of Coronary Artery Calcium Score for Coronary Artery Disease Screening among Severely Ill Liver Transplant Candidates: Case Series

Authors
Muhammad B. Hammami[1], Matthews Chacko[2], Haris Muhammad[3], Aliaksei Pustavoitau[4], Nicole Rizkalla[4], Saleh Alqahtani[1], Tinsay Woreta[1], Ruhail Kohli[1], Benjamin Philosophe[5], Andrew M. Cameron[5], Ahmet Gurakar[1]

Affiliations
[1]Division of Gastroenterology and Hepatology, Johns Hopkins University School of Medicine, Baltimore, MD, USA.
[2]Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, MD, USA.
[3]Department of Internal Medicine, Greater Baltimore Medical Center, Baltimore, MD, USA.
[4]Department of Critical Care and Anesthesiology, Johns Hopkins University School of Medicine, Baltimore, MD, USA.
[5]Division of Transplant Surgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

Corresponding Author:
Ahmet Gurakar, M.D.
Division of Gastroenterology and Hepatology. The Johns Hopkins University School of Medicine, 720 Rutland Avenue Ross Research Building, Suite 918 Baltimore, MD 21205.
E-mail: aguraka1@jhmi.edu
Phone Number: 410-614-3369
Fax Number: 443-683-8349

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Abstract

Noninvasive cardiac stress testing is essential to screen liver transplant (LT) candidates for the presence of coronary artery disease (CAD). However, cardiac stress testing may not be clinically feasible in some patients, especially among those who require intensive care for an extended period of time, before being listed for LT. The utility of coronary artery calcium (CAC) score as a potential noninvasive screening test for CAD among critically ill intensive care unit (ICU)-bound LT recipients who are unable to undergo conventional cardiac stress testing has not been well studied. We hereby report 4 LT recipients who were screened for CAD with only a CAC score before listing for LT. Our results suggest that CAC score may be a useful test to screen for CAD in severely ill ICU-bound LT recipients with low risk for coronary heart disease, who are unable to undergo cardiac stress testing. Such recipients requiring intensive care, with a CAC score of 0 Agatston units may safely forgo cardiac stress testing prior to LT. Future prospective studies with a larger sample size and longer follow-up would be helpful to validate our preliminary findings.

Key words: end stage liver disease; liver transplantation; heart diseases; coronary artery disease; coronary artery calcium score; mortality

Introduction:

Noninvasive cardiac stress testing is essential to screen liver transplant (LT) candidates for the presence of coronary artery disease (CAD) [1]. However, cardiac stress testing may not be clinically feasible in some cases, especially among severely ill patients who require intensive care for an extended period of time before listing for LT. Coronary artery calcium (CAC) score has been suggested as an alternative test for the diagnosis of CAD [2]. The utility of CAC score as a potential noninvasive screening test for CAD among LT recipients who are unable to undergo conventional cardiac stress testing has not been well studied. We hereby report 4 LT recipients who were screened for CAD with only a CAC score before listing for LT.

Methods:

We retrospectively reviewed the medical records of all patients who underwent cadaveric LT at Johns Hopkins Comprehensive Transplant Center, between April 2018 and March 2020 and only had a CAC score for CAD screening, prior to listing for LT. The data on demographics, cardiovascular risk factors, presence of chronic kidney disease (CKD), liver disease etiology, the need for renal replacement therapy (RRT) and/or vasopressor support at the time of listing for LT and CAC score were collected. Additionally, the incidence of a coronary heart disease (CHD) event during post-LT follow up was recorded. A CHD event was defined as myocardial infarction, definite angina or probable angina followed by revascularization, resuscitated cardiac arrest or CHD death. CAC score was estimated by non-contrast, electrocardiography-gated computed tomography and reported as the Agatston (A) score.

Patients and Results:

There were 4 recipients, all females. Three were Caucasian and 1 Asian. Two underwent LT alone and 2 underwent simultaneous liver-kidney (SLK) transplantation. All were referred for urgent LT evaluation due to a high MELD score and were managed in the intensive care unit (ICU) during the workup period. All 4 had labile hemodynamics (including 3 requiring vasopressor support) and 3 were on RRT (including 1 with CKD) at the time of listing. Median (range) age was 52 (45-61) years, BMI 26.1 (17.4-31.5) kg/m2, and MELD score 35 (30-37). Three patients had alcohol-related liver disease (2 of them had less than 6 months of sobriety) and one had drug-induced acute liver failure (ALF). Only the recipient with ALF had the triad of diabetes mellitus, hypertension, and dyslipidemia. Only one of the three alcohol-related liver disease recipients had a history of tobacco smoking, whereas the remaining two had no risk factors for cardiac disease. All recipients had undergone transthoracic echocardiogram and had normal right and left ventricular function with left ventricular ejection fraction ranging between 65-75%. Three of the four recipients had a CAC score of 0A and one of 1.3A. Three of the 4 recipients, including the one with a CAC score of 1.3A, had a follow-up of more than 600 days, whereas one recipient had a follow-up of 147 days. There were no CHD events observed (**Table 1**).

Recipient	**1**	**2**	**3**	**4**
CAC score	0	0	0	1.3
Age	48	55	45	61
Gender	Female	Female	Female	Female
Race	Caucasian	Caucasian	Caucasian	Asian
Liver Disease Etiology	Alcohol*	Alcohol**	Alcohol*	DILI
Transplant Type	Liver	SLK	SLK	Liver
Smoking Pack-year	0	0	12.5	0
DM	No	No	No	Yes
HLD	No	No	No	Yes
HTN	No	No	No	Yes
BMI	31.5	21.2	17.4	31
CKD	No	Yes	No	No
RRT	Yes	Yes	Yes	No
Vasopressor	Yes	Yes	Yes	No
LVEF	65-70%	70-75%	65-70%	65-70%
Survival (Days)	147	609	654	679

CAC coronary artery calcium, DILI drug-induced liver injury, SLK simultaneous liver-kidney transplantation, DM Diabetes Mellitus, HLD hyperlipidemia, HTN hypertension, BMI body mass index, CKD chronic kidney disease, RRT renal replacement therapy, LVEF left ventricular ejection fraction

* Less than 6 months of sobriety

** More than 6 months of sobriety

Discussion:

The prevalence of CAD among LT candidates is at least as frequent as in the general population [1]. No consensus exists regarding the best approach to screen for CAD in LT recipients [1, 3]. The American Association for the Study of Liver Disease recommends noninvasive cardiac testing with stress echocardiography for all adult LT candidates [1]. In contrast, a joint guideline from the American College of Cardiology Foundation/American Heart Association advocates non-invasive stress testing in patients with multiple CAD risk factors and further evaluation if necessary [3], where having ≥ 3 CAD risk factors is a reasonable threshold to prompt stress testing [4]. These risk factors include age > 60 years, prior cardiovascular disease, hypertension, dyslipidemia, diabetes mellitus, smoking, and left ventricular hypertrophy [3]. Three of the four recipients (75%) in our cohort were at low risk for CHD. All four recipients were female and only one recipient (25%) was above the age of 60. None of the recipients had nonalcoholic fatty liver disease as the etiology of their liver disease. Only one recipient (25%) had the triad of diabetes mellitus, hypertension, and dyslipidemia. In addition, only one recipient (25%) was a smoker and CKD was present only in one recipient (25%).

Dobutamine stress echocardiography (DSE) is frequently used as the initial screening test [1]. However, the majority of patients with advanced liver disease may be on pharmacological therapy like beta-blockers and would fail to reach a sufficient heart rate [1]. Myocardial perfusion imaging by single-photon emission computed tomography (SPECT) can be used as an alternative test [1]. However, its utility is limited since most patients with advanced liver disease have decreased arterial vascular resistance which limits the typical vasodilatory response of the coronary arteries to the vasodilating agents [5]. Evaluation of CAD is even more challenging among severely ill liver transplant candidates requiring intensive care, for whom cardiac stress testing may not be clinically feasible, especially those requiring continuous RRT and/or vasopressor support. All four recipients in our cohort were severely ill, had advanced liver disease, and required intensive care due to labile hemodynamics. Three of the four recipients (75%) were on RRT and vasopressor support before listing for LT. Although coronary angiography (CAG) is the gold standard test for the diagnosis of obstructive CAD, it is an invasive test and generally avoided among advanced liver disease patients unless necessary, given the risk of contrast related renal injury and the risk of bleeding associated with thrombocytopenia and coagulopathy [5].

Noninvasive coronary imaging with coronary artery calcium quantification has been suggested as an alternative test for the diagnoses and prognosis of CAD in the general population [2]. CAC score is a computed tomographic assessment of the calcium deposits in coronary arteries [2]. It was shown to be predictive of both low and high risk of coronary atherosclerosis and has been implemented in the screening of asymptomatic patients especially with an intermediate risk [2]. CAC score values are

generally classified as absent (0A), minimal (1–10A), mild (11–100A), moderate (101–400A) or extensive (>400A) [6]. Three of the four recipients (75%) had a CAC score of 0A and one (25%) had a CAC score of 1.3A. The incidence of CHD events was 0% in all four recipients who completed 147 days of follow up as well as in all three recipients who completed 600 days of follow up. It has been shown that CAC scoring has high negative predictive value (about 98%), and a score of 0 is strongly associated with the absence of any significant coronary obstructive lesion and indicates that the patient has a low risk of cardiovascular disease [7, 8]. In addition, CAC scoring has been shown to be a strong predictor of future incidence of cardiovascular events across different races beyond traditional risk factors [9]. Although non-calcified coronary plaque can cause significant coronary obstructive lesions, non-calcified lesions are uncommon in patients with a CAC score of 0A [10, 11].

The available data regarding the utility of CAC score among LT recipients is limited. Two studies with limited sample size have demonstrated the association between pre-LT CAC score and cardiac catheterization findings among liver transplant candidates [12, 13]. A CAC score with a cut-off value of 243A predicted occult CAD with a 90% sensitivity and 50% specificity [12]. A low CAC score (<100A) was found to successfully predict negative stress testing whereas a high CAC score (>400A) was predictive of obstructive CAD on CAG in asymptomatic LT candidates [13]. Further, it has been shown that preoperative CAC score is associated with early postoperative cardiovascular complications in LT recipients and a high CAC score (>400A) successfully predicted cardiovascular events during the first month following LT [14]. Furthermore, male sex, increasing age, and diabetes mellitus were predictors of a CAC score >400 in liver transplant recipients [15]. Other alternative non-invasive cardiac imaging to screen for CAD in LT candidates include computer tomographic coronary angiography (CTCA) and cardiovascular magnetic resonance imaging (CMRI) [16]. CTCA was reported to have a high sensitivity (98-99%) and specificity (89-91%) in detecting coronary artery plaques [16], with a high negative predictive value above 95% for excluding significant CAD [16, 17]. Major limitations to CTCA are nephrotoxicity from contrast administration especially in patients with concomitant renal dysfunction and the need for relative bradycardia [17]. CMRI was proposed as an integrated modality to evaluate cardiac function, stress response, structure, and coronary disease [17]. A recent study reported that a negative CMRI stress examination had 100% CAD event-free survival at 12 months [18]. Major limitations to stress CMRI are failure to reach appropriate heart rate response and contraindications to use vasodilator agents [19].

In conclusion, although CAC score has limited predictive value as a single screening test for CAD, it can be used to separate recipients with minimal risk of CAD (CAC score of 0A) from those who have more advanced disease. Our results suggest that CAC score may be a useful test to screen for CAD in severely ill ICU-bound LT recipients with low risk for CHD, who are not candidates for cardiac stress testing. Such

recipients requiring intensive care, with a CAC score of 0A may safely forgo cardiac stress testing prior to LT. However, this may not apply to recipients with high risk for CHD; since three of our four recipients had a CAC score of 0, were less than 60 years of age, and had a low risk for CHD. Future prospective studies with a larger sample size and longer follow-up would be helpful to validate our preliminary findings.

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