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High Coronary Artery Calcium Score Is Associated With Increased Major Adverse Cardiac Events After Liver Transplantation

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Background. Liver transplantation (LT) candidates frequently have multiple cardiovascular risk factors, and cardiovascular disease is a major cause of morbidity and mortality after LT. Coronary artery calcium (CAC) scores are a noninvasive assessment of coronary artery disease using computed tomography. This study examines CAC scores and cardiac risk factors and their association with outcomes after LT. **Methods.** Patients who underwent LT between January 2010 and June 2019 with a pretransplant CAC score were included in this study. Patients were divided by CAC score into 4 groups (CAC score 0, CAC score 1–100, CAC score 101–400, CAC score >400). Major adverse cardiovascular events (MACEs) were defined as myocardial infarction, stroke, revascularization, heart failure, atrial fibrillation, and cardiovascular death. Associations between CAC score and MACE or all-cause mortality within the 5-y post-LT follow-up period were analyzed using Cox regression. Statistical significance was defined as $P < 0.05$. **Results.** During the study period, 773 adult patients underwent their first LT, and 227 patients met our study criteria. The median follow-up time was 3.4 (interquartile range 1.9, 5.3) y. After 5 y, death occurred in 47 patients (20.7%) and MACE in 47 patients (20.7%). In multivariable analysis, there was no difference in death between CAC score groups. There was significantly higher risk of MACE in the CAC score >400 group, with a hazard ratio 2.58 (95% confidence interval 1.05, 6.29). **Conclusions.** CAC score was not associated with all-cause mortality. Patients with CAC score >400 had an increase in MACEs within the 5-y follow-up period compared with patients with a CAC score = 0. Further research with larger cohorts is needed to examine cardiac risk stratification in this vulnerable patient population.

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Cardiovascular disease is a leading cause of morbidity and mortality after liver transplantation (LT),[1,2] and coronary artery disease (CAD) is rising among LT candidates.[3] Patients with end-stage liver disease (ESLD) often have comorbidities that increase their risk of cardiovascular disease, including diabetes, hypertension, hyperlipidemia, and obesity. In fact, nonalcoholic fatty liver disease is the fastest growing etiology of liver disease worldwide and is associated with metabolic syndrome and increased cardiovascular risk.[4] Additionally, LT surgery itself presents a significant stressor. After LT, immunosuppressive therapy, hypertension, and renal compromise contribute to increased cardiovascular risk as well.[5] Accurate assessment of cardiovascular risk is crucial for appropriate management of patients pre- and post-LT.

There is a paucity of data to guide pre-LT cardiovascular risk assessment. The 2012 American Heart Association guidelines recommend noninvasive stress testing for LT candidates with 3 or more traditional CAD risk factors.[6] Ischemic evaluation with exercise stress testing is often limited by patients' ability to achieve the target heart rate. The 2013 American Association for the Study of Liver Disease guidelines recommend pharmacological stress testing with adenosine, dipyridamole, or dobutamine in patients unable to undergo exercise stress testing.[7] Dobutamine stress echocardiography (DSE), however, has also been shown to have low sensitivity and poor positive predictive value.[8-11] Single-photon emission computed tomography (SPECT) stress testing may also have limited utility in part because of chronic vasodilatory state in patients with ESLD, with a low sensitivity and high false-negative rate.[12,13] Thus, coronary artery angiography (invasive or noninvasive) remains the gold standard for the evaluation of CAD.[14] However, patients with ESLD often have tenuous renal function, and even noninvasive coronary angiography (coronary CT angiography [cCTA]) can worsen renal function.

Coronary artery calcium (CAC) score is a noninvasive assessment of CAD using CT. A noncontrast CT is relatively low cost, on average, only $85 to $125 without insurance coverage.[15] In comparison, Medicare reimbursement ranges from $63 to $91 for DSE and $62 to $444 for SPECT.[16] Studies have shown that low CAC scores are associated with very low cardiac event rate.[17] High CAC scores (>400 Agatston units) are predictive of significant CAD requiring revascularization[18] and are also predictive of cardiovascular complications in the first month after LT.[19] In this study, we evaluate the association between CAC score and long-term outcomes after LT.

MATERIALS AND METHODS

Patient Population

We performed a retrospective cohort study of patients who underwent their first LT at Johns Hopkins Hospital (JHH) between January 1, 2010, and June 30, 2019. Adult patients undergoing their first LT with an available pretransplant CAC score within 3 y of LT were included in this study. Patients with a history of major adverse cardiac events (MACEs) before transplant were excluded from the study. We also randomly selected 50 recipients of the first liver transplant during the same time frame who did not have a pretransplant CAC score as our comparator group for baseline patient characteristics.

Outcomes and Definitions

Primary outcomes for this study were all-cause mortality and MACE. We defined MACE as myocardial infarction (elevated troponin with either chest pain or ischemic electrocardiogram changes), coronary artery revascularization, stroke, hospitalization for heart failure, atrial fibrillation, or cardiovascular death.

Pretransplant Cardiac Evaluation

At JHH, pretransplant cardiovascular evaluation starts with a thorough history, physical examination, a standard 12-lead ECG, and screening transthoracic echocardiography for all candidates. Candidates with cardiovascular risk factors, including age >40, additionally undergo routine stress testing, either by dobutamine or SPECT combined with CT testing. Patients with abnormal or ischemic findings on stress testing or multiple cardiovascular risk factors may undergo further evaluation based on recommendations by the transplant committee cardiologist. Possible testing modalities include CAC score measurement, cCTA, or coronary artery angiograms. All patients are seen by the comprehensive transplant center multidisciplinary team. Of note, the transplant committee cardiologist changed during the study period between 2010 and 2019, resulting in institutional changes in the indication and decrease in the frequency of coronary artery angiograms. CAC scores were obtained primarily from CT images performed specifically for CAC scoring or from calculations from routine SPECT/CT protocol images, as previously described.[20] Several CAC scores were also calculated from a cCTA, as previously described.[21,22]

Statistical Analysis

For baseline characteristics, the chi-square and Fisher exact tests were used to compare proportions, and 1-way analysis of variance was used to compare means of CAC groups. Cox regression was used to analyze overall survival and MACE-free survival. Data were censored at 5 y of follow-up, given an increased loss to follow-up and limited data reliability after this time frame. Literature review and Akaike's information criterion were aided in our selection of factors for inclusion in the statistical model for multivariable analysis using Cox regression. We selected age, sex, diabetes, and hypertension as covariates. Kaplan-Meier plots were used to compare survival between groups. Statistical analyses were performed in Stata SE (Stata Corporation, College Station, TX; version 17).

Ethical Review

The Johns Hopkins University Institutional Review Board approved our study protocol under IRB00193544.

RESULTS

Between January 1, 2010, and June 30, 2019, 717 adult patients underwent their first liver transplant at JHH. Our study cohort included 227 recipients, of which 34% were women, and the mean age was 58.1 y (Table 1). The mean model for ESLD score at transplant was 20.7 (SD, 11.4). The most common etiology of liver disease was hepatitis C (50.7%), followed by alcohol (30.4%), nonalcoholic steatohepatitis (18.9%), hepatitis B (4.9%), and autoimmune (4.9%). The remaining 7.5% of cases included polycystic liver and kidney disease, alpha-1 antitrypsin deficiency, hemochromatosis,

TABLE 1.

Baseline characteristics of patients undergoing first liver transplantation at Johns Hopkins Hospital between January 2010 and June 2019, stratified by CAC score group

	Overall (N = 227)	CAC 0 (n = 60)	CAC 1–100 (n = 74)	CAC 101–400 (n = 45)	CAC >400 (n = 48)	*P*
Age, mean (SD), y	58.1 (6.8)	55.8 (8.2)	58.4 (5.8)	59.6 (5.9)	58.9 (6.5)	0.024
Sex (female), n (%)	78 (34.4)	28 (46.7)	28 (37.8)	13 (28.9)	9 (18.8)	0.017
BMI, mean (SD), kg/m^2	29.5 (5.8)	29.2 (5.9)	28.8 (5.9)	30.8 (5.8)	29.5 (5.4)	0.926
Biologic MELD, mean (SD)	20.7 (11.4)	19.8 (10.5)	19.4 (11.4)	22.4 (11.6)	22.3 (12.3)	0.712
Hypertension, n (%)	141 (62.1)	36 (60.0)	45 (60.8)	28 (62.2)	32 (66.7)	0.899
Dyslipidemia, n (%)	41 (18.1)	9 (15.0)	15 (20.3)	4 (8.9)	13 (27.1)	0.121
Diabetes, n (%)	94 (41.4)	25 (41.7)	27 (36.5)	18 (40.0)	24 (50.0)	0.525
CKD, n (%)	53 (23.4)	11 (18.3)	16 (21.6)	11 (24.4)	15 (31.2)	0.445
Smoking, n (%)						
Current	47 (20.7)	8 (13.3)	16 (21.6)	10 (22.2)	13 (27.1)	0.351
Former	92 (40.5)	21 (35.0)	28 (37.8)	22 (48.9)	21 (43.8)	0.476
Never	88 (38.8)	31 (51.7)	30 (40.5)	13 (28.9)	14 (29.2)	0.046
Liver disease etiology, n (%)[a]						
Alcohol	69 (30.4)	12 (20.0)	19 (25.7)	19 (42.2)	19 (39.6)	0.033
Hepatitis C	115 (50.7)	26 (43.3)	42 (56.8)	23 (51.1)	24 (50.0)	0.147
Hepatitis B	11 (4.8)	3 (5.0)	2 (2.7)	5 (11.1)	1 (2.1)	0.493
NASH	43 (18.9)	12 (20.0)	14 (18.9)	7 (15.6)	10 (20.8)	0.921
Autoimmune	11 (4.9)	7 (11.7)	2 (2.7)	2 (4.4)	0 (0)	0.026
Other	20 (7.5)	5 (8.3)	8 (10.8)	0 (0)	3 (6.3)	0.157
HCC, n (%)	93 (41.0)	22 (36.7)	36 (48.7)	19 (42.2)	16 (33.3)	0.327
Donor type, n (%)						
Deceased donor	173 (76.2)	46 (76.7)	57 (77.0)	36 (80.0)	34 (70.8)	0.764
Living donor	17 (7.4)	6 (10.0)	6 (8.1)	2 (4.4)	3 (6.2)	0.730
Simultaneous liver-kidney	37 (16.3)	8 (13.3)	11 (14.9)	7 (15.6)	11 (22.9)	0.561

[a]Can have multiple categories.

BMI, body mass index; CAC, coronary artery calcium; CKD, chronic kidney disease; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; NASH, nonalcoholic steatohepatitis.

TABLE 2.

Baseline cardiac history of patients undergoing first LT at Johns Hopkins Hospital between January 2010 and June 2019, stratified by CAC group

	Overall (N = 227)	CAC 0 (n = 60)	CAC 1–100 (n = 74)	CAC 101–400 (n = 45)	CAC >400 (n = 48)	*P*
CAD, n (%)	26 (11.5)	1 (1.7)	4 (5.4)	4. (8.9)	17 (35.4)	<0.001
PVD, n (%)	2 (0.9)	0 (0)	1 (1.4)	0 (0)	1 (2.1)	0.590
Aspirin, n (%)	25 (11.0)	6 (10.0)	10 (13.5)	4 (8.9)	5 (10.4)	0.859
Statin, n (%)	21 (9.3)	4 (6.7)	4 (5.4)	4 (8.9)	9 (18.8)	0.074
Exercise stress, n (%)	71 (31.2)	24 (40.0)	28 (37.8)	13 (28.9)	6 (12.5)	0.009
Dobutamine stress test, n (%)	127 (56.0)	32 (53.3)	44 (59.5)	28 (62.2)	23 (47.9)	0.473
SPECT/CT, n (%)	111 (48.9)	28 (46.7)	35 (47.3)	20 (44.4)	25 (52.1)	0.804
LHC, n (%)	39 (17.2)	1 (1.7)	4 (5.4)	8 (17.8)	26 (54.2)	<0.001
>50% stenosis	18 (46.2)	0 (0)	3 (75)	2 (25)	13 (50)	
LVEF, mean (SD)	62.8 (5.5)	62.6 (6.1)	62.1 (4.8)	62.6 (5.5)	64.3 (5.6)	0.313
Diastolic dysfunction, n (%)	111 (48.9)	28 (46.7)	37 (50.0)	20 (44.4)	26 (54.2)	0.982
CAC, median (IQR)	51.2 (0.3, 290)	0 (0,0)	27.5 (6.9, 59.7)	179.2 (148.9, 243.6)	802.1 (573.1, 1151.7)	<0.001
Days between CAC and LT, median (IQR)	215 (73, 381)	232.5 (67, 399)	223 (88, 403)	179 (46, 381)	160.5 (22, 282)	0.205

CAC, coronary artery calcium score; CAD, coronary artery disease; IQR, interquartile range; LHC, left heart catheterization; LT, liver transplantation; LVEF, left ventricular ejection fraction; PVD, peripheral vascular disease; SPECT/CT, single-photon emission computed tomography/computed tomography.

drug-induced liver injury, and primary hyperoxaluria. Most patients underwent deceased-donor LT (76.2%), with 16.3% simultaneous liver-kidney transplantation and 7.4% living-donor LT. The median follow-up time after LT was 3.4 y (interquartile range [IQR] 1.9, 5.3).

Between CAC score groups, there were statistically significant differences in age and sex, with patients in higher CAC score groups more likely to be older and male (Table 1). Higher CAC score groups also had a higher percentage of alcohol and autoimmune-related liver disease.

The median time between CAC score and date of LT was 215 d (IQR 73, 381). The median CAC score was 51.2 (IQR 0.3, 290) (Table 2): 60 recipients (26.4%) had a CAC score of 0, 74 (32.6%) had CAC scores 1 to 100, 45 (19.8%) had CAC scores 101 to 400, and 48 (21.1%) had CAC scores >400. Overall, 62.1% had a history of hypertension, 18.1% had

dyslipidemia, 41.4% had diabetes, 23.4% had chronic kidney disease, and 61.2% were current or former smokers. Patients in lower CAC score groups were more likely to never be smokers. Patients in higher CAC score groups were more likely to have a history of CAD. In our study cohort, 11.0% were taking aspirin at the time of LT, and 9.3% were taking a statin. There was a trend toward increased statin use with higher CAC scores. The mean left ventricular ejection fraction was 62.8%, and diastolic dysfunction was seen in 48.9% of patients, with no significant difference between CAC score groups.

The median follow-up time was 3.4 (IQR 1.9, 5.0) y. During the 5-y follow-up period, death occurred in 47 patients (20.7%), and MACE occurred in 47 patients (20.7%) (Table 3). Atrial fibrillation was the most common post-LT cardiovascular event (11%), followed by ischemic disease (7%), including revascularization and MI, and stroke (5%). The Kaplan-Meier plots also demonstrated lower MACE-free survival of the CAC score >400 group compared than the other CAC score groups (Figure 1). In multivariable analysis, there was no difference in death between CAC groups (Table 4). There was significantly higher risk of MACE in the CAC score >400 group compared than in the CAC score = 0 group, with a hazard ratio 2.58 (95% confidence interval 1.05, 6.29).

Compared with the group without pretransplant CAC scores, our study subjects were older and more likely to have a history of hypertension, diabetes, chronic kidney disease, and known CAD. They were also more likely to be taking aspirin (**Table S1, SDC**, http://links.lww.com/TXD/A482). Study subjects were also more likely to have nonalcoholic steatohepatitis–related cirrhosis. MACE was higher in study subjects, whereas death was not significantly different between the 2 groups (**Table S2, SDC**, http://links.lww.com/TXD/A482).

DISCUSSION

Assessment of cardiovascular risk in patients undergoing LT is crucial for both pretransplant evaluation and posttransplant management. However, exercise and pharmacologic stress testing have limited utility in the LT population, and coronary angiography remains the gold standard for evaluating CAD, despite associated risks. Our retrospective study examines the association between pretransplant CAC score and long-term outcomes after LT.

Overall, within 5 y after LT, MACE occurred in 20.7% of our patients, and all-cause mortality occurred in 20.7% of patients. Reported rates of MACE and mortality after LT vary greatly between prior studies. For example the reported rate of cardiac events >1 y after transplant ranges from 3.5% to 30.3%.[23-29] Reported survival at 5 y after LT has been reported to range from 67% to 82%.[23,24,28,29] These discrepancies are likely due to differing definitions of cardiac events, as well as differences in study populations.

In our study, high pre-LT CAC scores (>400) were associated with an increased risk of MACE during the 5-y follow-up period compared with a CAC score of 0. This association remained statistically significant after adjusting for age, sex, diabetes, and hypertension. CAC score was not significantly associated with death within 5 y after LT. In the high CAC score group, stroke was the most prevalent adverse event (12.5%), followed by atrial fibrillation (8.3%). Ischemic heart disease, including myocardial infarction (6.3%) and cardiac revascularization (4.2%), was responsible for 10.5% of adverse cardiac events. Our study is one of the first to show that a high pre-LT CAC score is associated with long-term adverse cardiac outcomes after LT.

Prior studies have shown that high CAC scores are associated with cardiovascular risk factors and obstructive CAD on coronary angiography.[18,30] One study found that CAC scores >400 were associated with an increased risk of cardiovascular events during the first month after LT.[19] Importantly, in patients with obstructive CAD who undergo appropriate revascularization, post-LT survival is not significantly different than patients without obstructive CAD.[31-34] In our study, patients underwent coronary angiography based on cardiology consultants' recommendations, and patients who underwent percutaneous coronary intervention or CABG prior to the study were not included in the final cohort. Of the 7 patients excluded because of PCI or CABG prior to LT, CAC score ranged from 129 to 2149 with a median 904 (IQR 365, 1114). Notably, of these 7 patients, 6 underwent DSE before transplant, all of which were normal, highlighting the low sensitivity of this test that has been described in prior studies.[8-11] High CAC scores of patients included in the study may represent nonrevascularizable lesions, nonobstructive CAD, or other risk factors for post-LT cardiac events.

Models for cardiac risk stratification in the liver transplant population are limited. In a study of 202 Swedish patients by Josefossen et al, renal impairment, age >52 y, and QTc prolongation were found to be predictive of cardiac events 1 y after LT.[27] Umphrey et al derived a model using the maximum achieved heart rate during dobutamine stress echocardiogram and the model for ESLD score to predict cardiac events 4 mo post-LT.[35] These studies were limited by a small sample size and

TABLE 3.

Five-year outcomes of death and MACE after liver transplantation, stratified by pretransplant CACS group, in patients who underwent first liver transplantation at Johns Hopkins Hospital between January 2010 and June 2019

	Overall (N = 227)	CACS 0 (n = 60)	CACS 1–100 (n = 74)	CACS 101–400 (n = 45)	CACS >400 (n = 48)
Deaths, n (%)	47 (20.7)	13 (21.7)	12 (16.2)	7 (15.6)	15 (31.25)
MACE, n (%)	47 (20.7)	8 (13.3)	11 (14.86)	13 (28.9)	15 (31.25)
Myocardial infarction	11 (4.8)	2 (3.3)	3 (4.1)	3 (6.7)	3 (6.3)
Stroke	12 (5.3)	3 (1.3)	3 (4.1)	0 (0.0)	6 (12.5)
Revascularization	5 (2.2)	0 (0.0)	0 (0.0)	3 (6.7)	2 (4.2)
Heart failure	4 (1.8)	1 (1.7)	0 (0.0)	2 (4.4)	1 (2.1)
Atrial fibrillation	25 (11.0)	6 (10.0)	5 (6.8)	10 (22.2)	4 (8.3)
Circulatory death	4 (1.8)	1 (1.7)	0 (0.0)	1 (2.2)	2 (4.2)

CACS, coronary artery calcium score; MACE, major adverse cardiac event.

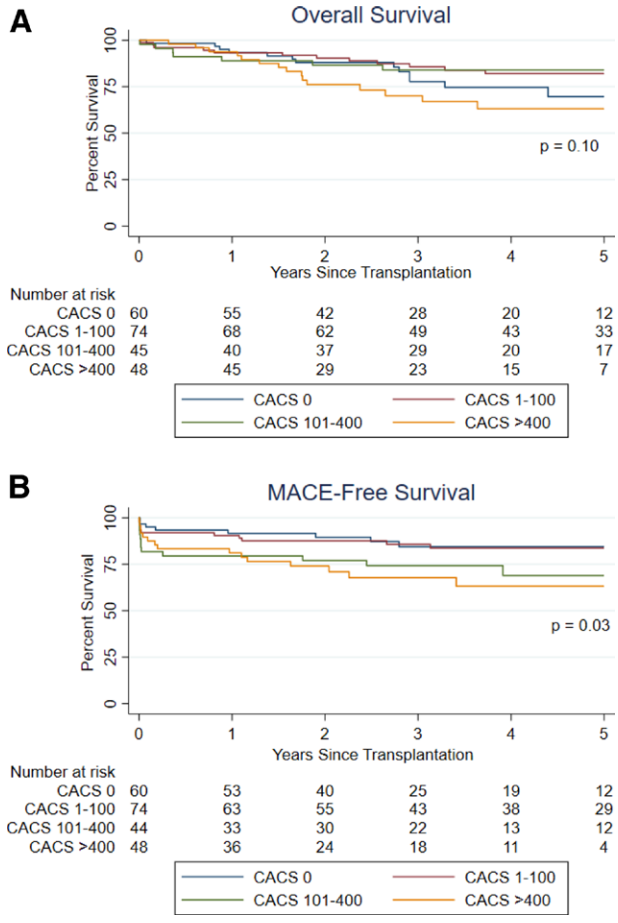

FIGURE 1. Survival. Kaplan-Meier plots for 5-y (A) overall survival and (B) MACE-free survival after liver transplantation, stratified by CACS group. CACS, coronary artery calcium score; MACE, major adverse cardiac event.

limited generalizability. Recently, the CAR-OLT risk score for cardiovascular risk stratification has demonstrated efficacy in predicting a 1-y risk of death or hospitalization from a major cardiac or vascular event after LT (C-statistic 0.78). The CAR-OLT algorithm includes 12 pretransplant clinical characteristics, including socioeconomic factors and a history of atrial fibrillation, respiratory failure, pulmonary hypertension, hepatocellular carcinoma, diabetes, and heart failure.[36] The CAR-OLT risk score has not yet been validated with a multicenter study, but it is a promising method for cardiac risk stratification in liver transplant candidates. Notably, VanWagner et al did not include CAC score in characteristic selection or in the final algorithm for the CAR-OLT study. Additionally, cardiac outcomes were evaluated only up to 1 y post-LT.

Our study has several limitations. First, the study population included only patients with pretransplant CAC scores, which may have resulted in selection bias. Many patients included in our study had a CAC score calculated from SPECT/CT. Patients without SPECT/CT may have instead obtained dobutamine stress testing, or they may have been younger with fewer risk factors, and thus did not undergo cardiac stress testing. Comparing our study group to 50 randomly selected LT patients without pre-LT CAC scores demonstrated that the study group was sicker, with a higher prevalence of baseline cardiovascular risk factors. Additionally, we ascertained

TABLE 4.

Multivariable Cox regression for association between CACS group and 5-y outcomes of death and MACE after liver transplantation

Cox regression—death (multivariable)	HR	95% CI
CACS		
CACS 0 (control)		
CACS 1–100	0.62	(0.28, 1.37)
CACS 101–400	0.59	(0.23, 1.51)
CACS >400	1.39	(0.64, 3.03)
Age	1.04	(0.99, 1.09)
Sex	1.02	(0.54, 1.92)
Diabetes	0.95	(0.52, 1.73)
Hypertension	1.19	(0.63, 2.25)
Cox regression—MACE (multivariable)		
CACS		
CACS 0 (control)		
CACS 1–100	1.04	(0.42, 2.61)
CACS 101–400	1.99	(0.79, 4.97)
CACS > 400	2.58	(1.05, 6.29)
Age	1.04	(0.99, 1.10)
Sex	0.81	(0.43, 1.51)
Diabetes	1.17	(0.64, 2.16)
Hypertension	0.87	(0.46, 1.61)

CACS, coronary artery calcium score; CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiac event.

MACEs based on chart review, which could be limited if patients subsequently presented to external hospitals for which we do not have access to electronic medical records. Finally, our study is limited by our relatively small sample size, which may have led to insufficient power to detect statistically significant differences between groups. Although at a large academic center, this is a single-center study, and future studies would need to evaluate the generalizability of our findings.

In conclusion, our study showed that high pre-LT CAC scores were associated with MACEs within the 5-y post-LT follow-up period. Incorporating a pre-LT CAC score may be helpful in cardiac risk stratification of LT candidates, both to identify high-risk individuals and inform the potential need for more invasive testing. Additionally, it is worth noting that CAC scores can be calculated from several tests that these patients may be undergoing already, such as SPECT/CT and cCTA, and therefore may not necessitate increased medical cost or radiation exposure. Future prospective studies with larger sample sizes are needed to confirm whether evaluation using a pre-LT CAC score can help improve cardiac risk stratification and post-LT outcomes.

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