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The Utility of Noninvasive PET/CT Myocardial Perfusion Imaging in Adult Liver Transplant Candidates

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Background. The optimal cardiovascular (CV) risk stratification in liver transplant (LT) candidates remains unclear. The aim of this study was to evaluate concordance of findings between dobutamine stress echocardiography (DSE), positron emission tomography/computed tomography myocardial perfusion imaging (PET/CT MPI), and left heart catheterization in adult LT candidates. **Methods.** Data on 234 consecutive adult LT candidates from February 2015 to June 2018 with PET/CT MPI were reviewed. Adverse CV outcomes were adjudicated via chart review by a board-certified cardiologist. **Results.** Median age was 60.8, body mass index 30.2 kg/m^2, and model of end-stage liver disease–sodium 14; 61% were male, and 54% had diabetes. Thirty-seven percent had nonalcoholic steatohepatitis and 29% alcohol-related liver disease. Sixty-five percent of patients had a DSE, of which 41% were nondiagnostic. No factors were independently associated with having a nondiagnostic DSE. The median global myocardial flow reserve correlated positively with hemoglobin and negatively with model of end-stage liver disease–sodium, age, ejection fraction, and body mass index. Moderate/high-risk MPIs were associated with older age and known CV disease. In patients with 2 cardiac testing modalities, findings were concordant in 87%. Eleven of 53 LT recipients experienced an adverse CV outcome, but no independent predictors were identified for this outcome. **Conclusions.** Results of different cardiac risk-stratification modalities were concordant across modalities the majority of the time in LT candidates, although these findings were not independently correlated with risk of post-LT CV outcomes. Given the high rates of nondiagnostic DSEs in this population, PET/CT MPI may be the preferred CV risk-stratification modality in older patients and those with known CV disease.

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INTRODUCTION

With advances in therapy for hepatitis C virus and the evolving obesity epidemic nonalcoholic steatohepatitis (NASH) and alcoholic liver disease have become the leading indications for liver transplantation (LT) in the United States.[1,2] Cardiovascular (CV) complications remain a major source of morbidity and mortality in LT recipients, but the optimal approach to risk stratify LT candidates for CV outcomes remains unknown.[3,4] The 2013 American Association for the Study of Liver Diseases guidelines recommend noninvasive cardiac evaluation before LT with echocardiography (ECHO) and noninvasive stress testing with cardiology evaluation if cardiac risk factors are present.[5] Dobutamine stress ECHO (DSE) is the primary stress test used in most centers, although LT candidates frequently cannot achieve the target heart rate and other concerns have been raised about the sensitivity and specificity of DSE findings.[6] In contrast, the American Society of Transplantation recommends a coronary computed tomography (CT) angiogram (CTA) or a traditional angiogram among patients with at least 2 risk factors for coronary artery disease (CAD).[7,8] Although practice patterns vary dramatically, overall use of cardiac catheterization remains low in most centers.

Cardiac positron emission tomography/CT myocardial perfusion imaging (PET/CT MPI) is a noninvasive technique that may address some of the shortcomings of DSE in LT candidates, including those who are obese or unable to achieve the targeted heart rate. PET/CT MPI assesses for functional CAD including myocardial flow reserve (MFR). MFR has been correlated with risk of CV outcomes in nontransplant patients.[9-13] There are emerging data that PET/CT MPI may have superior diagnostic accuracy (sensitivity 81%–89%, negative predictive value 87%–94%) compared with CT angiography for coronary ischemia.[14] PET/CT MPI is also very attractive in this population given that it has no nephrotoxicity and is not affected by chronic vasodilation that limits other modalities of functional CAD testing. To date, there have been limited data regarding the performance characteristics of PET/CT MPI in risk stratification of LT candidates, although some studies demonstrate lower MFR in patients with decompensated cirrhosis.[15-17] The aim of this study was to assess the concordance of findings between DSE, PET/CT MPI, and left heart catheterization (LHC) in adult LT candidates and the utility of incorporating PET/CT MPI in a cardiac risk-stratification algorithm for high-risk LT candidates. Concordance was defined as having the same risk-stratification categorization (ie, low risk versus moderate/high risk) across different testing modalities. Secondary aims were to identify correlates of risk of 6-mo post-LT CV outcomes.

MATERIALS AND METHODS

Patient Population

This was a retrospective cohort study of adult LT candidates at a tertiary academic medical center evaluated between February 1, 2015, and June 1, 2018, under our new cardiac risk-stratification algorithm (Figure 1). In 2015, our center incorporated PET/CT MPI along with a 2D cardiac ECHO for LT candidates with 2 or more risk factors: age ≥60, body mass index (BMI) >35, diabetes, atrial fibrillation, pacemaker or left bundle branch block, history of coronary revascularization, or stroke. This modality was chosen because of its superior sensitivity and specificity compared with single-photon emission tomography (SPECT) and potential benefits compared with cardiac magnetic resonance imaging.[18,19] Details of our PET/CT MPI protocol have been outlined elsewhere. Briefly, individuals were asked to fast 8 h prior and to abstain from caffeine. A lose-dose CT scan was performed with perfusion imaging.[20] Individuals who did not meet criteria for PET/CT MPI as the initial cardiac risk-stratification test underwent DSE. Those who had a nondiagnostic DSE then underwent PET/CT MPI. Candidates with moderate/high-risk findings on DSE or PET/CT MPI were referred to cardiology to determine the role for additional testing including coronary angiography via LHC. The managing transplant hepatologist could order additional testing outside of this algorithm if they deemed it medically necessary. Our center performs approximately 60 to 80 LT/y. An IRB waiver of consent was obtained. Clinical information was abstracted using EMERSE, an automated electronic health record search tool, and manual review of clinic notes.[21] Any patient that underwent PET/CT MPI as part of their LT evaluation was eligible for inclusion in the study.

Data Collection

Demographic data (age at time of PET/CT MPI, sex, race, ethnicity), etiology of liver disease, presence of hepatocellular carcinoma, medical comorbidities (diabetes, cardiac disease, chronic kidney disease), tobacco use, and BMI were collected. Any patient listed as "cryptogenic cirrhosis" was reclassified in the NASH/nonalcoholic fatty liver disease category based on prior literature supporting NASH being the likely underlying cause of liver disease in these patients.[22] Labs at time of imaging were abstracted. Results of standard ECHO and DSE were recorded, as were results of PET/CT MPI including MFR. For any patient that underwent cardiac catheterization,

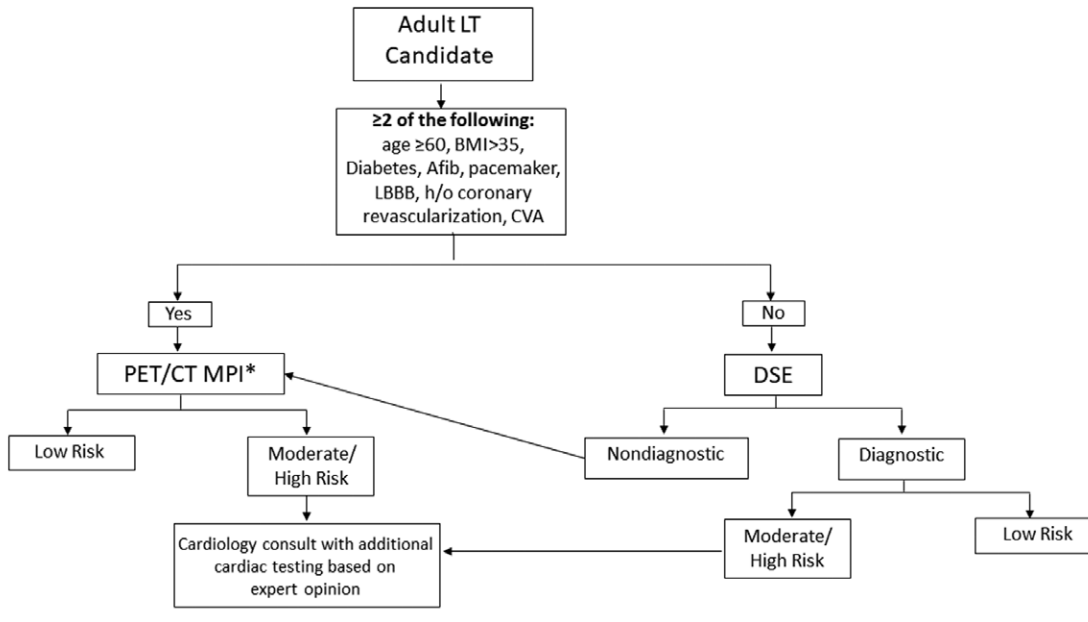

FIGURE 1. Cardiac risk-stratification algorithm. Afib, atrial fibrillation; BMI, body mass index; CVA, cerebrovascular accident; DSE, dobutamine stress echocardiography; LBBB, left bundle branch block; LT, liver transplant; PET/CT MPI, positron emission tomography/computed tomography myocardial perfusion imaging.

results of these studies were also noted. DSE was categorized first as being a diagnostic or nondiagnostic study and second according to the presence of inducible ischemia. PET/CT MPI studies were categorized as being "low" or "medium/high risk" for future cardiac events based on the interpretation by the reading expert nuclear cardiologist. LHC findings were categorized as normal coronaries/nonobstructive coronary disease versus findings needing intervention based on expert interventional cardiology assessments and recommendations. Concordant cardiac risk-stratification testing was defined as having 2 testing modalities that categorized the findings as either both low risk or both moderate/high risk.

CV Outcomes Within 6 Mo of LT

LT recipients were evaluated for specific CV outcomes defined as a composite of acute coronary syndrome (ACS), arrhythmias (ventricular tachycardia/fibrillation, atrial fibrillation/flutter, symptomatic heart block), heart failure, or transient ischemic attack/stroke within first 6 mo of LT. ACS was assessed as a separate outcome in isolation. All outcomes were adjudicated by a board-certified cardiologist.

Statistical Analysis

Descriptive and bivariate analyses were performed to assess baseline and time of LT characteristics. Chi-square tests and Fisher exact tests were used for categorical variables, and *t* tests were used for continuous variables. Variables with distributions that deviated from normality were reported by median and interquartile range (Q1, Q3) and were compared using the Kruskal-Wallis test. *P* values ≤0.05 were considered statistically significant. Multivariate analysis was conducted using linear and logistic regression. All analyses were performed in STATA 14 (StataCorp, College Station, TX).

RESULTS

Baseline Characteristics

A total of 234 adult patients underwent PET/CT MPI during the study period. The baseline characteristics of the cohort are displayed in Table 1. The median age was 60.8 y, 61.5% were men, and 87% were Caucasian. The leading etiology of cirrhosis was NASH (37.6%) followed by alcohol (29.1%). Hepatocellular carcinoma was present in 19.7% of LT candidates. The median BMI at time of imaging was 30.2 kg/m^2, and 54.4% had diabetes. The prevalence of other cardiac risk factors varied, with hypertension (53.6%), CAD (23.4%), and hyperlipidemia (29.8%) being most prevalent. The median model of end-stage liver disease–sodium (MELD-Na) at time of imaging was 14.

DSE/ECHO Results

Overall results of pre-LT cardiac testing are shown in Table 1 and Figure 2. The median ejection fraction was 65%, and right ventricular systolic pressure was 30 mm Hg. Moderate/severe valvular heart disease was infrequent (6.8%; 10 aortic stenosis, 2 mitral regurgitation, 4 tricuspid regurgitation), as was moderate/severe diastolic dysfunction (5.9%). Diastolic dysfunction was defined using the standard criteria of the American Society of Echocardiography.[23] Overall, 64.9% of LT candidates underwent DSE, and 40.7% of these studies were considered nondiagnostic, primarily because of cavity obliteration requiring early termination of dobutamine infusion. On univariate analyses, there were no factors found to be associated with having a nondiagnostic DSE. Among those with a diagnostic study, the vast majority were assessed as having low-risk findings (ie, no evidence of inducible ischemia).

PET/CT MPI Results

Overall, 32 of the 234 (13.6%) LT candidates had moderate/high-risk findings for inducible ischemia on PET/CT MPI. The characteristics of LT candidates with low-risk versus moderate/high-risk PET/CT MPI findings are shown in Table 1. The pattern of different cardiac risk-stratification testing results categorized by low-risk versus moderate/high-risk PET/CT MPI are outlined in Figure 2. On univariate analysis, having a moderate/high-risk PET/CT MPI was associated with older age, history of CAD, hypertension, congestive heart failure, hyperlipidemia, lower hemoglobin, and lower total bilirubin; however, on multivariate analysis, only older age (odds ratio 1.06; 95% confidence intervals, 1.00-1.13; $P = 0.04$) and history of CAD (odds ratio 5.74; 95% confidence intervals, 2.37-13.88; $P \leq 0.001$) were independently associated with having moderate/high-risk findings on PET/CT MPI. Subjects who had a moderate/high-risk PET/CT MPI were less likely to be listed for LT (17.4% versus 30.3%) and also die (34.4% versus 20.2%), though not at a statistically significant level.

MFR data were available in 203 of the 234 cases. The median MFR on PET/CT MPI was low at 1.79, and 52 (26%) had an MFR <1.5, which is considered very abnormal.[24] On univariate analysis, MFR was negatively correlated with age, male sex, left ventricular ejection fraction (LVEF), BMI, international normalized ratio, total bilirubin, creatinine, and MELD-Na. MFR was positively correlated with hemoglobin and albumin. Those with a moderate/high-risk CT/PET MPI had significantly lower MFRs (1.5 versus 1.8). On multivariate analysis, age, LVEF, BMI, and MELD-Na remained negatively correlated with MFR, and hemoglobin remained positively correlated with MFR (Table 2).

Cardiac Catheterization Results and Concordance of Testing

A total of 41 (17.5%) patients underwent a LHC, with 14 (34.2%) having moderate/high-risk findings. Interestingly, an abnormal LHC requiring intervention was noted in a similar proportion of those with a moderate/high-risk PET/CT MPI compared with those with a low-risk PET/CT MPI (9 of 21 = 43% versus 8 of 20 = 40%) (Figure 2).

Only 22 (9.4%) patients had all 3 tests (PET/CT MPI, DSE, and LHC) performed for risk stratification, only 15 of which had diagnostic tests for all 3 testing modalities (Table 3). Six of these 15 patients had concordant findings across all 3 of these tests, and 9 were concordant among 2 modalities but discordant across the third modality.

Overall, 116 patients had at least 2 different diagnostic cardiac risk-stratification tests. Among these 116 PET/CT MPI tests, 101 (87%) had concordant findings with at least 1 other diagnostic cardiac risk-stratification test (DSE or LHC) (Table 3). Among candidates who had a diagnostic DSE, results of DSE and PET/CT MPI were concordant in 84% of cases (76/90). Findings of PET/CT MPI and LHC were concordant 59% of the time (24/41). Among candidates with a diagnostic DSE who underwent LHC, results of these 2 tests were concordant 46% of the time (7/15). For reference, DSE is reported to have a sensitivity of 0% to 80% and coronary CTA of 33% to risk stratify patients for CV outcomes post-LT.[6]

TABLE 1.

Baseline characteristics of patients

	Overall cohort, N = 234	Moderate/high risk PET/CT MPI, N = 32	Low-risk PET/CT MPI, N = 202	*P*
Clinical characteristics		Median (IQR) or N (%)		
Age (y)	60.8 (54.6–65.6)	63.5 (59.6–66.5)	60.3 (54.0–65.5)	**0.009**
Male gender	144 (61.5%)	18 (56.2%)	125 (62.2%)	0.52
White race	205 (87.6%)	29 (87.2%)	175 (86.6%)	0.77
Etiology of liver disease				0.79
HCV	24 (10.3%)	4 (12.5%)	20 (9.4%)	
Alcohol	68 (29.1%)	7 (21.8%)	61 (30.3%)	
NASH	88 (37.6%)	14 (43.7%)	74 (36.8%)	
PBC/PSC	16 (6.8%)	3 (9.3%)	13 (6.4%)	
HCV/ETOH	17 (7.3%)	2 (6.2%)	15 (7.4%)	
HCC	33 (19.7%)	6 (28.5%)	27 (18.5%)	0.37
BMI (kg/m^2)	30.2 (26.5–35.2)	24 (24–24)	28.8 (24.3–32.7)	0.91
Diabetes	128 (54.4%)	16 (50%)	112 (55.4%)	0.56
History of tobacco use	146 (62.1%)	19 (59.4%)	126 (62.4%)	0.74
History of CAD or CVA	55 (23.4%)	20 (62.5%)	35 (17.3%)	**<0.001**
HTN	126 (53.6%)	25 (78.1%)	101 (50%)	**0.003**
Arrhythmia	36 (15.3%)	7 (21.8%)	29 (14.4%)	0.27
CHF	11 (4.6%)	4 (12.5%)	7 (3.4%)	**0.04**
Hyperlipidemia	70 (29.8%)	18 (56.2%)	52 (25.7%)	**<0.001**
Hemodialysis	11 (4.7%)	2 (6.2%)	9 (4.4%)	0.65
Dual L/K listing	12 (5.1%)	2 (6.2%)	10 (4.9%)	0.67
Transplant listing status (N = 198)				0.42
Listed	57 (28.8%)	4 (17.4%)	53 (30.3%)	
Ongoing evaluation	28 (14.1%)	4 (17.4%)	24 (13.7%)	
Not listed	113 (57.1%)	15 (65.2%)	98 (56.0%)	
Died pre-LT	52 (22.2%)	11(34.4%)	41 (20.2%)	0.08
Labs at imaging				
MELD-Na	14 (10–18)	12 (9–19)	14 (10–18)	0.87
Hemoglobin (g/dL)	11.5 (9.6–13.1)	10.6 (8.8–11.8)	11.5 (9.7–13.1)	**0.02**
Plt (10^3/mL)	90.5 (64–127)	102 (74–139)	90 (62.5–124.5)	0.30
ALT (U/L)	33 (25–50)	34.5 (25–46)	33 (25–51)	0.83
T Bilirubin (mg/dL)	1.9 (1.1–3.5)	1.1 (0.7–2.35)	2 (1.2–3.6)	**0.006**
Albumin (g/dL)	3.2 (2.9–3.6)	3.1 (2.7–3.6)	3.2 (2.9–3.6)	0.83
Sodium (mq/dL)	137.5 (135–140)	138.5(135.5–140)	137 (135–140)	0.39
Cr (mg/dL)	0.9 (0.76–1.37)	1.0 (0.8–1.4)	0.96 (0.75–1.3)	0.17
INR	1.2 (1.1–1.4)	1.2 (1.1–1.3)	1.2 (1.1–1.4)	0.07
Cardiac testing				
LVEF (%)	65 (60–70)	65 (60–67.5)	65 (60–70)	0.24
RVSP mm Hg	30 (25–35)	31.5 (26–38)	29 (25–35)	0.63
Moderate/severe diastolic dysfunction	14 (5.9%)	1 (3.1%)	13 (6.4%)	0.69
DSE				0.23
Not done	82 (35%)	13 (40.6%)	69 (34.2%)	
Low risk	85 (55.9%)	11 (34.4%)	74 (36.6%)	
Moderate/high risk	5 (3.3%)	2 (6.3%)	3 (1.4%)	
Nondiagnostic	62 (40.7%)	7 (21.8%)	56 (27.7%)	1.0
Did not achieve target HR	12 (19.1%)	1 (14.3%)	11 (19.6%)	
Hypotension	6 (9.5%)	1 (14.3%)	5 (8.9%)	
Cavity obliteration	27 (42.9%)	3 (43.8%)	24 (42.8%)	
Other/unspecified	18 (28.6%)	2 (28.5%)	16 (28.6%)	
MFR (N = 203)	1.79 (1.48–2.18)	1.50 (1.24–1.82)	1.80 (1.51–2.20)	**0.004**
Coronary artery calcium score Agatston units (N = 85)	279 (0–579)	436.5 (290.5–925.5)	172 (0–545)	0.12
DSE and PET/CT concordant	76 (84.4%)	2 (15.4%)	74 (96.1%)	**<0.001**
Left heart cath				**<0.001**
Not done	193 (83%)	11 (34.4%)	182 (90.1%)	
Low risk	27 (65.8%)	12 (44.4%)	15 (55.6%)	
Moderate/high risk	14 (34.2%)	9 (64.3%)	5 (35.7%)	

ALT, alanine aminotransferase; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; Cr, creatinine; CVA, cerebrovascular accident; DSE, dobutamine stress echocardiography; ETOH, alcohol; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HTN, hypertension; INR, international normalized ratio; L/K, liver kidney; LVEF, left ventricular ejection fraction; MELD, model of end-stage liver disease; MFR, myocardial flow reserve; MPI, myocardial perfusion imaging; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cholangitis; PET/CT, positron emission tomography/computed tomography; Plt, platelet; PSC, primary sclerosing cholangitis; RVSP, right ventricular systolic pressure.

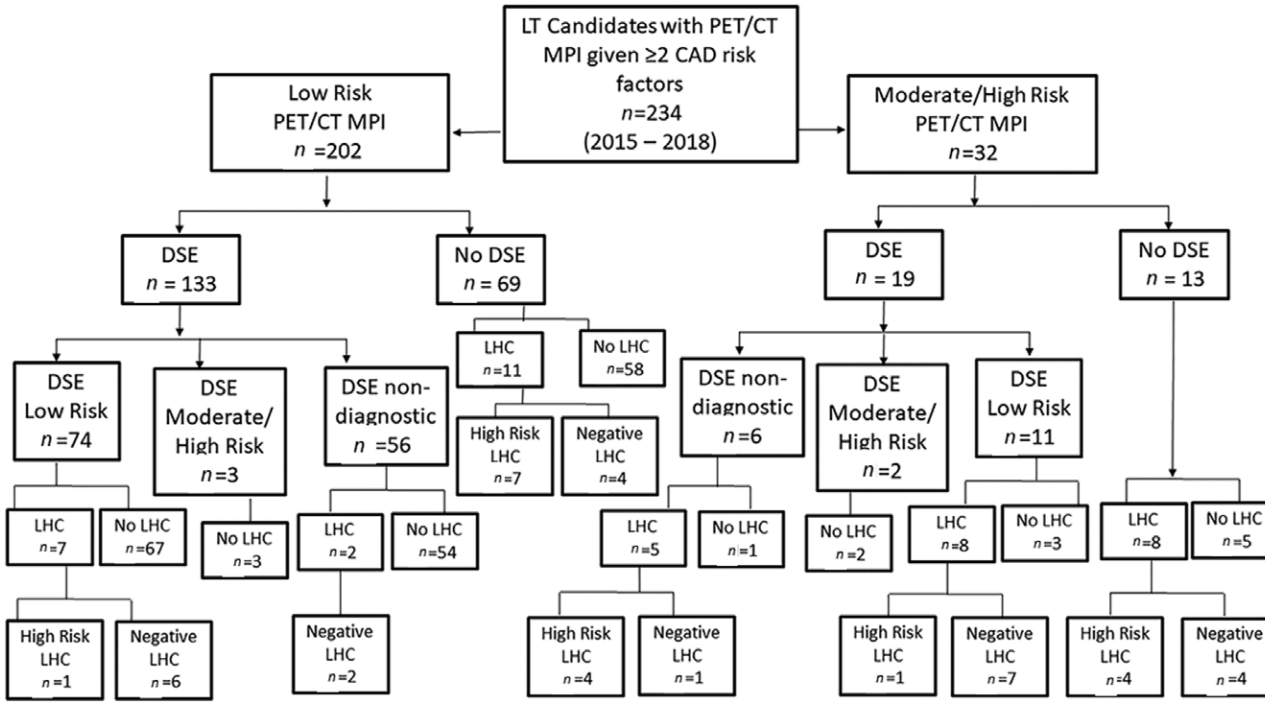

FIGURE 2. Flow diagram of cardiac testing results in adult LT candidates. CAD, coronary artery disease; DSE, dobutamine stress echocardiography; LHC, left heart catheterization; LT, liver transplant; PET/CT MPI, positron emission tomography/computed tomography myocardial perfusion imaging.

CV Outcomes Within 6 Mo of LT

A total of 53 patients underwent LT over the study period, and their characteristics at baseline, time of transplant, and cardiac testing results are shown in Table 4. A total of 11 patients (20.7%) met criteria for having a CV outcome within 6 mo of LT. Six patients had arrhythmias, 4 developed heart failure, and 1 had a transient ischemic attack/stroke. The median time from LT to cardiac outcome was 19.5 d (interquartile range 2.5–77). There were no significantly different characteristics at baseline to distinguish those who did versus did not have a post-LT CV outcome; however, those with a cardiac outcome did have lower serum alkaline phosphatase ($P=0.04$) and sodium ($P=0.02$) levels at time of LT. Notably, there were no statistically significant differences in results of cardiac testing among those who did versus those who did not have a cardiac outcome. Seven of the 11 (64%) patients with a post-LT cardiac event had a low-risk DSE, and 9 of 11 (82%) had a low-risk PET/CT MPI. Among the 2 patients with a cardiac event (both having arrythmias as their CV outcome) that underwent pre-LT LHC, both were categorized as having low-risk findings. Given that no patients had an ACS outcome, we could not evaluate for predictors of myocardial ischemic outcomes.

DISCUSSION

In light of the dramatic shift in the primary etiology of cirrhosis leading to LT evaluation, the risk profile of these candidates and the most frequent post-LT complications have also changed. CV outcomes post-LT will likely increase as NASH becomes the leading indication for transplant. To mitigate these risks, LT programs have sought to design pre-LT cardiac risk-stratification algorithms that balance the risks and

TABLE 2.

Variables associated with myocardial flow reserve

	Univariate			Multivariate		
Variable	**Coeff**	**95% CI**	***P***	**Coeff**	**95% CI**	***P***
Age	−0.01	−0.02 to 0.00	0.02	−0.01	−0.02 to 0.00	**0.005**
Sex	−0.25	−0.42 to −0.08	0.003	−0.14	−0.29 to 0.01	0.06
LVEF	−0.01	−0.02 to 0.00	0.006	−0.01	−0.02 to 0.00	**0.04**
BMI	−0.01	−0.02 to 0.00	0.02	−0.01	−0.02 to 0.00	**0.008**
Hg	0.13	0.09-0.16	<0.001	0.11	0.07-0.14	**<0.001**
INR	−0.56	−0.85 to −0.26	<0.001			
Tbili	−0.02	−0.04 to 0.00	0.03			
Albumin	0.22	0.07 to 0.38	0.004			
Cr	−0.13	−0.23 to −0.02	0.01			
MELD-Na	−0.02	−0.04 to −0.01	<0.001	−0.01	−0.02 to −0.00	**0.007**

BMI, body mass index; MELD, model of end-stage liver disease; Cr, creatinine; INR, international normalized ratio; LVEF, left ventricular ejection fraction; Tbili, total bilirubin; CI, confidence intervals.

TABLE 3.

Concordance of cardiac testing

	LHC normal coronaries/ nonobstructive CAD			LHC cardiac intervention recommended			LHC not performed			
	DSE			DSE			DSE			
PET/CT MPI	No inducible ischemia	Nondiagnostic	Not done	No inducible ischemia	Nondiagnostic	Not done	No inducible ischemia	Inducible ischemia	Nondiagnostic	Not done
Low risk	**6**[a]	**2**	**7**	***1***		4	**67**	3	54	58
Mod/high risk	***7***	1	4	***1***	**4**	**4**	3	**2**	1	5
Concordant low risk	PET/CT MPI + DSE	PET/CT MPI + LHC	DSE + LHC				Concordant Mod/High risk	PET/CT MPI + DSE	PET/CT + LHC	DSE + LHC
	74	15	6					2	9	1
Overall concordance	PET/CT MPI + DSE	PET/CT MPI + LHC	DSE + LHC	Patients with 2 concordant tests (PET/CT MPI + DSE, PET/CT MPI + LHC or DSE + LHC)						
	76/90 (84%)	24/41 (59%)	7/15 (46%)	101/116 (87%)						

Results that were concordant across at least 2 diagnostic studies are bolded. Results that were concordant across 2 diagnostic tests but discordant across the third are italicized.
[a]Results that were concordant across all 3 testing modalities.
CAD, coronary artery disease; DSE, dobutamine stress echocardiography; LHC, left heart catheterization; PET/CT MPI, positron emission tomography/computed tomography myocardial perfusion imaging.

benefits of different cardiac testing modalities. Current guidelines still rely heavily on DSE despite the limitations of this modality in LT candidates; however, the American College of Cardiology does not make a specific recommendation for the modality to be used to risk stratify LT candidates.[25] In our cohort, 41% of patients had a nondiagnostic or incomplete DSE. On the opposite end of the spectrum, some centers opt to perform cardiac catheterization in all or most potential LT candidates, but others are leery because of the risks of bleeding and contrast nephropathy.[26] In this study, we evaluated the use of different cardiac risk-stratification modalities after incorporating PET/CT MPI as a new screening modality in our patients with high-risk clinical features or suboptimal DSE. We demonstrated that, among patients undergoing 2 different cardiac risk-stratification tests, results were concordant 87% of the time. We then evaluated outcomes of patients who underwent LT to identify CV outcomes within 6 mo of LT and found that, among the 11 patients with an outcome, there were no distinguishing pretransplant features, and in particular, only 2 of 11 had a moderate/high-risk PET/CT MPI but low-risk LHC findings. This may highlight the underlying limitations of our screening tests to capture multifactorial contribution to risk beyond individual patient characteristics.

An important finding for clinical practice in our study was the very high rate of nondiagnostic DSE studies in this patient population. Overall, 40.7% of patients who underwent DSE were characterized as having nondiagnostic studies for a variety of reasons, including failing to achieve goal heart rate, hypotension, and cavity obliteration. Cavity obliteration can frequently manifest in cirrhotic cardiomyopathy, as it has similarities with hypertrophic cardiomyopathy and can have clinical impact on response to LT because of large volume shifts.[27] Our analysis did not reveal any factors associated with having a nondiagnostic study, making it challenging to identify patients in whom a DSE would be low yield. In this study protocol, a nondiagnostic DSE prompted PET/CT MPI to complete the cardiac evaluation, and thus, our overall percentage of nondiagnostic DSEs are likely higher than expected. From a healthcare utilization and cost perspective, it appears that this approach does not provide the necessary information for many patients. Having both a DSE and subsequently a PET/CT MPI is costly and time consuming and may prolong the time needed to make a decision about LT listing. Alternatively, the cost of PET/CT MPI is higher than DSE and is not routinely performed at many centers because of less availability of radiopharmaceuticals and imaging equipment. Future studies that investigate predictors of nondiagnostic DSE in this patient population can help optimize the CV risk-stratification algorithm for individual patients. Findings between DSE and PET/CT MPI or PET/CT MPI and cardiac catheterization were concordant 80% of the time. Our center does not perform LHC at high rates in LT candidates, and it is unclear if incorporating this more often would better characterize the remaining 20% of LT candidates. As we accrue more data over time, we hope to better refine the criteria prompting PET/CT MPI as the initial CV risk-stratification modality. Based on our data, older age and a history of CV disease, namely, CAD and hyperlipidemia, were strongly associated with having a moderate/high-risk PET/CT study. Therefore, incorporating these clinical risk factors as triggers for bypassing DSE for PET/CT in this population may be warranted.

Another interesting finding of note pertains to the median MFR in this population and the variables associated with MFR. MFR was independently negatively associated with increasing age, higher BMI, lower hemoglobin, and LVEF. Importantly, MELD-Na was strongly independently negatively associated with MFR, reflecting the unique pathophysiology of coronary blood flow in end-stage liver disease. Evaluating MFR among patients with cirrhosis may help better characterize cirrhotic cardiomyopathy. Future studies might consider not only taking into account the overall assessment from the PET/CT MPI (ie, low versus moderate/high risk for a cardiac event) but also the MFR in LT candidates when determining overall risk for CV outcomes post-LT. We may have failed to identify a relationship between MFR and post-LT CV outcomes given the small number of transplanted patients (N = 53) and cardiac outcomes (N = 11) in our cohort. In addition, the various cardiac risk-stratification modalities are best suited for evaluating risk of ischemic CV events, and our CV outcome definition included events beyond myocardial ischemia. It is not unsurprising that the rates of ischemic cardiac events post-LT

TABLE 4.

Transplanted patient characteristics and outcomes

Transplanted patients	Total transplants, N = 53	Cardiac outcome, N = 11	No cardiac outcome, N = 42	*P*
Age (y)	60.9 (52.1–65.5)	64.8 (51.2–68.0)	60.1 (52.7–65.0)	0.33
Male gender	45 (86.5%)	9 (81.8%)	36 (87.8%)	0.63
White race	47 (88.7%)	11 (100%)	0	0.32
Etiology of liver disease				0.47
HCV	4 (7.7%)	0	4 (9.7%)	
HBV	3 (5.7%)	0	3 (7.3%)	
Alcohol	13 (25%)	3 (27.7%)	10 (24.4%)	
NASH	17 (32.7%)	6 (54.5%)	11 (26.8%)	
PBC/PSC	3 (5.7%)	0	3 (7.3%)	
Other	10 (19.2%)	1 (9.1%)	9 (21.9%)	
HCV/alcohol	2 (3.8%)	1 (9.1%)	1 (2.4%)	
HCC	13 (37.1%)	4 (36.3%)	9 (37.5%)	1.0
Diabetes	28 (52.8%)	8 (72.7%)	20 (47.6%)	0.18
Tobacco	30 (56.6%)	7 (63.6%)	23 (54.7%)	0.73
History of CAD or CVA	10 (18.8%)	2 (18.2%)	8 (19.1%)	1.0
HTN	30 (56.6%)	8 (72.7%)	22 (52.4%)	0.31
Arrhythmia	14 (26.4%)	4 (36.3%)	10 (23.8%)	0.45
CHF	3 (5.6%)	1 (9.1%)	2 (4.7%)	0.51
Hyperlipidemia	15 (28.3%)	3 (27.3%)	12 (28.6%)	1.0
Hemodialysis	5 (9.4%)	2(18.2%)	3 (7.1%)	0.27
Dual L/K listing	7 (13.5%)	2 (18.2%)	5 (12.2%)	0.63
Transplant-specific data*				
Donor type: DCD	40 (97.6%)	0	1 (2.9%)	1.0
BMI at transplant (kg/m^2)	28.6 (24.3–32.7)	30.2 (28.1–33.7)	28.3 (24.1–32.5)	0.42
MELD-Na	20 (15–27)	18 (16–27)	20.5 (15–27)	1.0
Hemoglobin (g/dL)	9.25 (7.8–11.3)	8.1 (7.5–11)	9.5 (7.9–11.5)	0.37
Plt (10^3/mL)	75 (54–103)	71 (47–100)	83 (54–109)	0.60
ALT (U/L)	29 (24–48)	37 (20–48)	28.5 (25–54)	0.75
TBilirubin (mg/dL)	5.6 (2.1–11.1)	8.1 (2.7–10.6)	5.5 (1.8–11.7)	0.93
AlkP (U/L)	152 (111–190)	119 (67–144)	156 (113–197)	**0.04**
Albumin (g/dL)	3 (2.6–3.3)	2.9 (2.8–3.1)	3 (2.6–3.4)	0.48
Sodium (meq/L)	137 (133–140)	141(138–143)	136 (132–139)	**0.02**
Cr (mg/dL)	1.11 (0.79–1.69)	1.59 (0.82–1.69)	1.08 (0.76–1.68)	0.60
INR	1.5 (1.3–1.7)	1.6 (1.4–1.7)	1.5 (1.2–1.8)	0.97
Cardiac testing				
LVEF %	65 (60–70)	60 (59–70)	65 (60–70)	0.21
RVSP mm Hg	33 (25–39)	34 (33–39)	31 (24–39)	0.25
Moderate/severe diastolic dysfunction	3 (5.6%)	1 (9.1%)	2 (4.7%)	0.51
DSE	33 (65%)	8 (72.7%)	25 (59.5%)	0.29
Low risk	20 (60.1%)	7 (87.5%)	13 (52%)	
Moderate/high risk	1 (3%)	0	1 (4%)	
Nondiagnostic	12 (36.3%)	1 (12.5%)	11 (44%)	
PET/CT MPI				0.18
Low risk	49 (92.5%)	9 (81.8%)	40 (95.2%)	
Moderate/high risk	4 (7.5%)	2 (18.2%)	2 (4.7%)	
PET/CT MFR	1.63 (1.42–2.13)	1.5 (1.45–1.63)	1.73 (1.4–2.2)	0.24
Left heart cath	9(16.9%)	2 (18.2%)	7 (16.6%)	0.63
Low risk	6 (66.6%)	2 (100%)	4 (57.1%)	
Moderate/high risk	3 (33.3%)	0	3 (42.8%)	

*Labs and status at time of LT.

Bolded values indicate statistical significance.

AlkP, alkaline phosphatase; ALT, alanine aminotransferase; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; Cr, creatinine; CVA, cerebrovascular accident; DCD, donor after cardiac death; DSE, dobutamine stress echocardiography; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HTN, hypertension; INR, international normalized ratio; L/K, liver kidney; LT, liver transplant; LVEF, left ventricular ejection fraction; MELD, model of end-stage liver disease; MFR, myocardial flow reserve; MPI, myocardial perfusion imaging; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cholangitis; PET/CT, positron emission tomography/computed tomography; Plt, platelet; PSC, primary sclerosing cholangitis; RVSP, right ventricular systolic pressure.

were low 6-mo post-LT based on our risk-stratification protocol. Extending the outcome interval to 12-mo post-LT may have identified additional correlations between pre-LT factors and risk of CV outcomes post-LT.

There are several limitations to note in this study. First, it was a retrospective analysis, which is inherently subject to errors in data abstraction. Second, there is likely a referral bias for patients who underwent LHC, which makes it difficult to

correlate findings of noninvasive stress testing with cardiac catheterization findings. Third, the total number of patients who underwent LT was limited, which increased the risk of type II errors in analyses and reduced our ability to confidently identify risk factors for adverse CV outcomes and to improve risk stratification. Furthermore, we did not have data on the frequency of adverse CV outcomes in other LT recipients from our center who did not undergo a PET/CT MPI for comparison. Generalizability of our study may also be limited because of the fact that many centers have Tc-99m SPECT MPI available but not PET/CT MPI; however, prior studies of SPECT MPI in LT candidates have demonstrated conflicting data, with some studies showing that abnormal SPECT studies were associated with increase in overall mortality but not CV complications post-LT.[6] Despite these limitations, our work adds to the understanding of the pros and cons of different cardiac risk-stratification tools in this unique patient population and underscores the potential usefulness of MFR in assessing risk of CV outcomes. Specifically our study adds to the existing literature by evaluating PET/CT MPI in this unique patient population, as little to no data have been published on this topic to date. Future studies can continue to build on this work by evaluating CV outcomes up to 12-mo post-LT and by also evaluating intraoperative factors that may also impact risk of CV outcomes.

In conclusion, we demonstrated that findings across 2 different cardiac risk-stratification methods (PET/CT MPI with DSE or LHC) were concordant 80% of the time. Our data suggest that PET/CT MPI may be the preferred CV risk-stratification modality over DSE in patients with clinical risk factors and particularly in older patients and those with a history of CAD and other cardiac disease. These findings will need to be validated across different risk groups before implementation in clinical practice, however. Further studies examining the role of other specific cardiac parameters generated from PET/CT MPI (ie, MFR) may also help to refine cardiac risk-stratification algorithms given that an abnormal MFR has been associated with risk of CV outcomes in other patient populations.

REFERENCES

1. Wong RJ, Singal AK. Trends in liver disease etiology among adults awaiting liver transplantation in the United States, 2014-2019. *JAMA Netw Open*. 2020;3:e1920294.
2. Parrish NF, Feurer ID, Matsuoka LK, et al. The changing face of liver transplantation in the United States: the effect of HCV antiviral eras on transplantation trends and outcomes. *Transplant Direct*. 2019;5:e427.
3. VanWagner LB, Lapin B, Levitsky J, et al. High early cardiovascular mortality after liver transplantation. *Liver Transpl*. 2014;20:1306–1316.
4. Nicolau-Raducu R, Gitman M, Ganier D, et al. Adverse cardiac events after orthotopic liver transplantation: a cross-sectional study in 389 consecutive patients. *Liver Transpl*. 2015;21:13–21.
5. Martin P, DiMartini A, Feng S, et al. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Hepatology*. 2014;59:1144–1165.
6. Konerman MA, Fritze D, Weinberg RL, et al. Incidence of and risk assessment for adverse cardiovascular outcomes after liver transplantation: a systematic review. *Transplantation*. 2017;101:1645–1657.
7. Raval Z, Harinstein ME, Skaro AI, et al. Cardiovascular risk assessment of the liver transplant candidate. *J Am Coll Cardiol*. 2011;58:223–231.
8. VanWagner LB, Harinstein ME, Runo JR, et al. Multidisciplinary approach to cardiac and pulmonary vascular disease risk assessment in liver transplantation: an evaluation of the evidence and consensus recommendations. *Am J Transplant*. 2018;18:30–42.
9. Ziadi MC. Myocardial flow reserve (MFR) with positron emission tomography (PET)/computed tomography (CT): clinical impact in diagnosis and prognosis. *Cardiovasc Diagn Ther*. 2017;7:206–218.
10. Di Carli MF, Murthy VL. Cardiac PET/CT for the evaluation of known or suspected coronary artery disease. *Radiographics*. 2011;31:1239–1254.
11. Murthy VL, Bateman TM, Beanlands RS, et al. Clinical quantification of myocardial blood flow using PET: joint position paper of the SNMMI cardiovascular council and the ASNC. *J Nucl Cardiol*. 2018;25:269–297.
12. Murthy VL, Naya M, Foster CR, et al. Improved cardiac risk assessment with noninvasive measures of coronary flow reserve. *Circulation*. 2011;124:2215–2224.
13. Schindler TH, Schelbert HR, Quercioli A, et al. Cardiac PET imaging for the detection and monitoring of coronary artery disease and microvascular health. *JACC Cardiovasc Imaging*. 2010;3:623–640.
14. Danad I, Raijmakers PG, Driessen RS, et al. Comparison of coronary CT angiography, SPECT, PET, and hybrid imaging for diagnosis of ischemic heart disease determined by fractional flow reserve. *JAMA Cardiol*. 2017;2:1100–1107.
15. Famoso G, Ferrazzi E, Senzolo M, et al. Coronary microvascular dysfunction in patients with advanced liver cirrhosis: the missing piece of the puzzle for understanding cirrhotic cardiomyopathy? *Eur Heart J*. 2013;34(suppl_1).
16. Shum K, Englert J, Stewart M, et al. Characterization of myocardial blood flow in end stage liver disease patients undergoing liver transplant evaluation. *J Nucl Med*. 2019;60:162.
17. Yilmaz Y, Kurt R, Yonal O, et al. Coronary flow reserve is impaired in patients with nonalcoholic fatty liver disease: association with liver fibrosis. *Atherosclerosis*. 2010;211:182–186.
18. Bateman TM, Dilsizian V, Beanlands RS, et al. American society of nuclear cardiology and society of nuclear medicine and molecular imaging joint position statement on the clinical indications for myocardial perfusion PET. *J Nucl Cardiol*. 2016;23:1227–1231.
19. Mc Ardle BA, Dowsley TF, deKemp RA, et al. Does rubidium-82 PET have superior accuracy to SPECT perfusion imaging for the diagnosis of obstructive coronary disease? A systematic review and meta-analysis. *J Am Coll Cardiol*. 2012;60:1828–1837.
20. Ghannam M, Yun HJ, Ficaro EP, et al. Multiparametric assessment of left atrial remodeling using 18F-FDG PET/CT cardiac imaging: a pilot study. *J Nucl Cardiol*. 2020;27:1547–1562.
21. Hanauer DA, Mei Q, Law J, et al. Supporting information retrieval from electronic health records: a report of University of Michigan's nine-year experience in developing and using the Electronic Medical Record Search Engine (EMERSE). *J Biomed Inform*. 2015;55:290–300.
22. Caldwell SH, Lee VD, Kleiner DE, et al. NASH and cryptogenic cirrhosis: a histological analysis. *Ann Hepatol*. 2009;8:346–352.
23. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the american society of echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29:277–314.
24. Schindler TH. Myocardial blood flow: putting it into clinical perspective. *J Nucl Cardiol*. 2016;23:1056–1071.
25. Lentine KL, Costa SP, Weir MR, et al; American Heart Association Council on the Kidney in Cardiovascular Disease and Council on Peripheral Vascular Disease; American Heart Association; American College of Cardiology Foundation. Cardiac disease evaluation and management among kidney and liver transplantation candidates: a scientific statement from the American Heart Association and the American College of Cardiology Foundation: endorsed by the American Society of Transplant Surgeons, American Society of Transplantation, and National Kidney Foundation. *Circulation*. 2012;126:617–663.
26. Maddur H, Bourdillon PD, Liangpunsakul S, et al. Role of cardiac catheterization and percutaneous coronary intervention in the preoperative assessment and management of patients before orthotopic liver transplantation. *Liver Transpl*. 2014;20:664–672.
27. Isaak RS, Kumar PA, Arora H. PRO: transesophageal echocardiography should be routinely used for all liver transplant surgeries. *J Cardiothorac Vasc Anesth*. 2017;31:2282–2286.