Outcome of Liver Transplant Recipients With Revascularized Coronary Artery Disease: A Comparative Analysis With and Without Cardiovascular Risk Factors

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Background. Coronary artery disease (CAD) is a significant problem during evaluation for liver transplantation (LT). We aim to assess survival in LT recipients based on presence, severity, extent of CAD, and cardiac events within 90 days of LT. **Methods.** Eighty-seven LT recipients with history of pre-LT angiogram (December 2005 to December 2012) were compared with 2 control groups without prior angiogram, 72 LT recipients matched for cardiovascular risk factors (control group I), and 119 consecutive LT recipients without any CV risk factors (control group II). CAD was assessed by (1) vessel score ($\geq 50\%$ reduction in luminal diameter), and (2) Extent score (Reardon scoring system). **Results.** Of the 87 LT recipients (study group), 58 (66.7%) had none or less than 50% stenosis, 29 (33.3%) had obstructive CAD ($\geq 50\%$ stenosis), 7 (8%) with single-vessel disease, and 22 (25.3%) with multivessel disease. In the study group, irrespective of prerevascularization severity of CAD ($P = 0.357$), number of segments involved (0, 1-2, > 2 segments, $P = 0.304$) and extent of CAD based on Reardon score (0, 1-9, > 10 , $P = 0.224$), comparable posttransplant survival was noted. Overall, patient survival in the revascularized CAD group was comparable to angiogram group without obstructive CAD, and both control group I and control group II ($P = 0.184$, Log Rank). Postoperative cardiac events within 90 days of LT predicted poor survival in study group as well as control groups. **Conclusions.** Severity or extent of CAD does not impact post-LT survival, if appropriately revascularized. Early postoperative cardiac events are associated with inferior survival in LT recipients, irrespective of underlying CAD.

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Listing for liver transplantation (LT) in patients with known coronary artery disease (CAD) remains a challenge for transplant hepatologists and transplant surgeons. Postoperative outcome in LT recipients with CAD has been assessed in 2 recent studies with conflicting findings.^{1,2} Yong et al² reported that the presence of multivessel CAD, as opposed to the severity of CAD, was predictive of increased length of stay, postoperative pressor requirements, and significantly higher mortality. A second study, however, reported no difference in long-term survival in recipients with multivessel CAD compared to single vessel disease.¹ In addition, survival was not different after stratifying patients based on the severity of their CAD. These survival outcomes may have been skewed toward more favorable results as most centers adopt strict selection criteria with the lower-risk patients going for LT. The frequency of moderate or severe CAD in LT recipients, although varying depending upon the underlying etiology, has been reported in 13.3% of subjects with non-alcohol-related end-stage liver disease, with an overall prevalence as high as 16.2% in an earlier study.³ Vanwagner et al⁴ reported an increased prevalence of cardiovascular complications after LT, particularly in nonalcoholic steatohepatitis patients independent of usual cardiac risk factors, but this did not affect overall mortality. Further studies are needed to identify risk factors for poor

posttransplant outcome in LT recipients based on underlying disease etiology and severity of CAD.

The primary aim of this study is to assess posttransplant survival in LT recipients with angiographically proven but revascularized CAD based on presence and severity of CAD before revascularization. A secondary aim is to assess the risk of development of cardiac events within 90 days of LT in this study group, and its implication on posttransplant mortality.

MATERIALS AND METHODS

Patients being considered for orthotopic LT at the Methodist University Hospital Transplant Institute undergo a standard cardiac workup including a history, physical examination, electrocardiogram, chest X-ray, and transthoracic echocardiogram. In addition, moderate-risk patients, defined as older than 40 years and/or at least 1 cardiac risk factor undergo a pharmacological stress test. If patients are determined to be at high risk because of abnormal noninvasive testing, or an ejection fraction less than 60% in the setting of low systemic vascular resistance, they undergo further testing with coronary angiography. Adherence to this standard operating practice has varied over the years particularly in asymptomatic patients with negative stress test in the presence of concomitant medical problems, such as underlying renal dysfunction, severe coagulopathy, and/or urgency for LT. These cases are reviewed at the Multidisciplinary Listing Committee meeting, and further evaluation with angiogram is being made or waived on case by case basis on recommendation of the Multidisciplinary Listing Committee. The guidelines being used for coronary angiogram before LT at our center is outlined in Figure 1. Patients who are diagnosed with obstructive CAD undergo percutaneous revascularization as deemed appropriate by the treating cardiologist and are started on dual antiplatelet

therapy with aspirin and clopidogrel for the required duration before LT.

We identified 1535 end-stage liver disease patients consecutively evaluated for liver or liver and kidney transplantation at Methodist University Hospital Transplant Institute from December 2005 to December 2012; 154 of them had coronary angiogram. After exclusion of patients with retransplants ($n = 2$), prior renal transplants ($n = 1$), and those not listed ($n = 31$), records of 120 patients, who had angiogram, were reviewed. Eighty-seven of the 120 patients who underwent LT resulted in the study group for this analysis. Details of the patients who did not undergo LT until the end date of study group selection (December 2012) are summarized in Figure 2. Seventy-five (86.2%) of the 87 patients had a cardiac angiogram done within 12 months before their LT, 4 (4.6%) within 2 years, and 8 (9.25%) within 3 to 10 years prior to LT.

The control group I was obtained from LT recipients from December 2005 to December 2012 who did not undergo a cardiac angiogram. Using propensity matching score for outcome variables for age (stratified into groups: < 40 years, 40-59 years, ≥ 60 years), sex, calculated model for end-stage liver disease (MELD) score at listing (stratified into groups based on MELD score; < 15, 15-19, 20-24, 25-29, 30-34, > 35, and status 1A), body mass index (BMI) (stratified into groups as < 18.5, 18.5-24.9, 25-29.9, > 30), diabetes, hypertension, and smoking status, we created this control group which resulted in 72 controls for 87 cases. A second control group was obtained by selecting all consecutive patients seen within the same period who had no history of cardiovascular risk factors. Matching was not performed due to limited number of available cases.

Scoring for severity of CAD was performed with a scoring system described previously⁵ that was modified by

FIGURE 1. Standard operative practice for coronary angiogram before LT at Methodist University Hospital Transplant Institute.

FIGURE 2. Algorithm describing the inclusion and exclusion leading to the final analysis in the study group of 87 patients included in the study.

Reardon et al.⁶ CAD was assessed by (1) vessel score based on number of vessels with greater than 50% reduction in luminal diameter in any of the proximal coronary arteries on angiogram, and (2) extent score, based on a modified Reardon severity scoring system: less than 50% stenosis of the luminal diameter, 1 point; 50% to 74%, 2 points; 75% to 99%, 3 points; 100% or total obstruction, 4 points. The points for each lesion in the proximal coronary circulation were summed to come up with the score for severity.

LT recipients were divided into groups based on presence or absence of angiographically proven CAD; and their long-term survival was compared. Long-term patient survival was also assessed based on the severity of stenosis before revascularization intervention. All the angiographic images were independently reviewed by a single invasive cardiologist.

The occurrence of cardiac events within 90 days of LT was reviewed, and its effect on survival after LT was analyzed. Cardiac event was defined as acute coronary syndrome (ST or non-ST elevation myocardial infarction [STEMI]), congestive heart failure (CHF), and arrhythmia of any type that needed intervention (severe bradycardia, supraventricular tachycardia [SVT], atrial fibrillation, ventricular tachycardia, and pulseless electrical activity).

Routinely, our center has been using a steroid-free immunosuppression protocol which consisted of induction immunosuppression with rabbit-derived antithymocyte globulin and use of Tacrolimus as the primary immunosuppression in the posttransplant period. Mycophenolate mofetil is used for a total of 3 months and then discontinued unless the patient's primary disease is autoimmune hepatitis, primary biliary cirrhosis, or primary sclerosing cholangitis. Primary sirolimus or everolimus is used in lieu of tacrolimus if the recipient's creatinine level remained over 2.0 mg/dL beyond posttransplant day 7.

The University of Tennessee Health Science Center Institutional Review Board approved the study a priori.

STATISTICAL CONSIDERATIONS

Descriptive statistics were calculated for all of key variables. Continuous variables were expressed as mean with standard deviation and categorical variables as counts with percentages. One-way analysis of variance was used to compare the differences between mean values. Categorical variables were evaluated by Yates corrected χ^2 tests with Fisher exact tests. Univariate and multivariate logistic regressions were applied to identify significant predictors

TABLE 1.**Baseline characteristics of the angiogram and the nonangiogram groups (with and without CV risk-factor matching)**

Parameters	Angiogram group	Nonangiogram control group I	Nonangiogram control group II
	n (87)	n (72)	n (119)
Age at transplant: mean $\pm$ SD, y ^a	57.53 $\pm$ 7.3	51.9 $\pm$ 8.85	50.5 $\pm$ 12.6
Sex, male (%) ^b	62 (71.3)	54 (75.0%)	67 (56.3%)
BMI, mean $\pm$ SD ^a	30.0 $\pm$ 5.8	29.55 $\pm$ 4.82	25.03 $\pm$ 3.20
Race (white), N (%) ^a	72 (82.8)	50 (69.4%)	88 (73.9%)
MELD score, mean $\pm$ SD	17.7 $\pm$ 6.5	16.3 $\pm$ 6.1	18.8 $\pm$ 9.0
HCC, N (%)	25 (28.7)	17 (23.6%)	15 (19.0%)
ALT, mean $\pm$ SD, IU/mL	53.93 $\pm$ 61.92	55.38 $\pm$ 51.54	75.01 $\pm$ 94.21
INR, mean $\pm$ SD	1.61 $\pm$ 0.51	1.68 $\pm$ 0.51	1.81 $\pm$ 0.83
Total bilirubin, mean $\pm$ SD, mg/dL ^a	4.49 $\pm$ 5.97	4.94 $\pm$ 7.53	7.74 $\pm$ 8.86
Serum Cr, mean $\pm$ SD, mg/dL	1.39 $\pm$ 1.03	1.16 $\pm$ 0.67	1.21 $\pm$ 1.01
Hypertension, N (%) ^a	29 (33.3)	27 (37.5%)	0 (0%)
Diabetes, N (%) ^a	34 (39.1)	25 (34.7%)	0 (0%)
Lipid profile, mean $\pm$ SD			
Total cholesterol, mg/dL	150 $\pm$ 56	135 $\pm$ 51	160 $\pm$ 81
TG, mg/dL	100 $\pm$ 55	99 $\pm$ 59	108 $\pm$ 69
LDL, mg/dL	81 $\pm$ 42	72 $\pm$ 34	91 $\pm$ 68
HDL, mg/dL	42 $\pm$ 22	39 $\pm$ 17	41 $\pm$ 26
History of smoking, N (%) ^a	45 (51.7)	34 (47.2%)	0 (0%)

^a $P < 0.05$.^b $P < 0.01$.

Control group I: Matched for CV-risk-factors (age, gender, MELD score, BMI, diabetes, hypertension, smoking status), Control group II: Consecutive patients without any CV-risk-factors.

for the occurrence of cardiac events within 90 days. Time to death was calculated from the LT date to the date of death and those who were still alive were censored at their last contact date. Kaplan-Meier method was used to estimate patient survival, and the log-rank test was used to compare the distributions at the levels of a given clinical factor of interest. Cox proportional hazard model was used to assess predictors of mortality. In multivariable

survival models, we kept in mind the “10 events per covariate” recommendation^{7,8} to decide how many predictors can be supported in such models. Using this assumption for 36 events (death) in the angiogram group, the model could only support 4 predictors. As such, using somewhat liberal entry ($P < 0.1$), we assessed significant predictors of mortality in a multivariate model. Proportional hazards assumption of the Cox Model was further confirmed

TABLE 2.**Clinical and demographic profile of the LT recipients with and without obstructive CAD**

Parameters	Nonobstructive CAD (n = 58)	Obstructive CAD (n = 29)	P
Age at transplant: mean $\pm$ SD, y	55.7 $\pm$ 7.2	61.2 $\pm$ 6.2	0.001
Sex, male (%)	41 (70.7%)	21 (72.4%)	0.867
BMI, mean $\pm$ SD	30.2 $\pm$ 6	29.7 $\pm$ 5.4	0.715
Tobacco use, N (%)	31 (53.4)	15 (51.7)	0.879
Active	21 (36.2)	11 (37.9)	
Past use	10 (17.2)	4 (13.8)	
None	27 (46.6)	14 (48.3)	
MELD, mean $\pm$ SD	18.79 $\pm$ 18.79	15.44 $\pm$ 6.58	0.033
HCC, N (%)	13 (22.4)	12 (41.4)	0.065
ALT, IU/mL	60 $\pm$ 74	42 $\pm$ 25	0.740
INR, mean $\pm$ SD	1.7 $\pm$ 0.5	1.4 $\pm$ 0.5	0.005
Total bilirubin, mean $\pm$ SD, mg/dL	5.5 $\pm$ 7	2.6 $\pm$ 2.2	0.002
Serum Cr, mean $\pm$ SD, mg/dL	1.4 $\pm$ 1	1.3 $\pm$ 1	0.566
Hypertension, n (%)	18 (31)	11 (38)	0.520
Diabetes, n (%)	19 (33)	15 (52)	0.087
HbA1c, mean $\pm$ SD	5.5 $\pm$ 1.4	5.5 $\pm$ 1	0.129
Lipid profile, mean $\pm$ SD			
Total cholesterol, mg/dL	151 $\pm$ 58	149 $\pm$ 53	0.972
TG, mg/dL	94 $\pm$ 54	112 $\pm$ 56	0.094
LDL, mg/dL	82 $\pm$ 45	80 $\pm$ 37	0.960
HDL, mg/dL	44 $\pm$ 24	37 $\pm$ 17	0.200

TABLE 3.**Frequency and severity of CAD in patients with angiographically defined CAD with $\geq 50\%$ luminal stenosis**

Parameters	Frequency of CAD	Severity score
	N = 29	
Single vessel disease	7 (24.1%)	
Multivessel disease	22 (75.9%)	
Combined Reardon severity score	—	11.28 $\pm$ 8.86
Left main	2 (6.9%)	0.3 $\pm$ 0.71
LAD (junction of middle and distal one third)	16 (55.2%)	1.83 $\pm$ 1.7
LAD (proximal one third of septal branch)	1 (3.4%)	0.14 $\pm$ 0.74
LAD (proximal one third diagonal branch)	6 (20.7%)	0.7 $\pm$ 1.34
Proximal one third of the obtuse marginal branch of the CFX	10 (34.5%)	0.9 $\pm$ 1.31
CFX	7 (24.1%)	0.66 $\pm$ 1.1
RCA (up to and the origin of the PDA)	16 (55.2%)	1.9 $\pm$ 1.6
Proximal one third of PDA	3 (10.3%)	0.3 $\pm$ 0.9

^a Severity of CAD is based on Reardon score.⁶

graphically using a plot of survival curves based on the Cox model and Kaplan-Meier estimates for each group. The level of statistical significance for analyses was set at *P* less than 0.05 unless otherwise stated. All statistical analyses were performed with SPSS version 21 (IBM corporation, Armonk, NY).

RESULTS

Baseline differences in the angiogram (study group), and the 2 nonangiogram groups (control group I—matched for cardiovascular risk factors and control group II—not matched for any cardiovascular risk factors) are summarized in Table 1. Obvious differences were noted, particularly with CV risk factors (BMI, diabetes, hypertension, and history of smoking) among the 3 groups, considering the control groups are selected differentially: one matched for CV risk factors (control group I), and the second not matched for CV risk factors. Mean age at LT was statistically different among the 3 groups (*P* = 0.01), with higher in the angiogram group (57.53 $\pm$ 7.3) compared with the other 2 groups. Higher proportions of whites were noted in the angiogram group compared with the nonangiogram control group I

(72 [82.8%] vs 50 [69.4%]). MELD score, HCC frequency, ALT, INR, serum Cr, total Cholesterol, triglyceride (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were not significantly different among the 3 groups (Table 1).

In the 87 patients (study group) who had a coronary angiogram, 61 (71.3%) were men and predominantly of white descent [72 (82.8%)]. Hepatitis C was the most common etiology for LT (46%), followed by nonalcoholic steatohepatitis/cryptogenic cirrhosis (27.6%), ethyl alcohol (14.9%), α -1-antitrypsin (4.6%), hepatitis B (2.3%), primary sclerosing cholangitis (1.1%), Wilson disease (1.1%), and was unknown (1.1%) in 1 patient.

Of all the patients who underwent a coronary angiogram, 58 (66.7%) patients had normal or nonobstructive CAD, and 29 (33.3%) patients had obstructive CAD ($\geq 50\%$ stenosis). Of the 29 patients, 22 (25.3%) of them had revascularization procedures at various time points before their LT, 10 had history of coronary artery bypass graft (3 of them had percutaneous coronary intervention [PCI]/stent during their pretransplant period) and 12 without any history of CABG had revascularization procedure with PCI/stent. Patency of the stents and coronary arteries were confirmed in

TABLE 4.**Cardiac events in the LT recipients with and without obstructive CAD**

	Angiogram group (n = 87)		Nonangiogram group I (n = 72)	Nonangiogram group II (n = 119)
Cardiac events	Obstructive CAD (n = 29)	No CAD (n = 58)		
All cardiac events	8	15	8	6
Atrial Fibrillation	3	11	5	3
SVT	0	1	1 ^a	1
Bradycardia	1 ^b	1	0	0
CHF	0	1 ^c	1	0
NSTEMI	2 ^d	1	0	0
AMI	2	0	0	1
PEA	0	0	1	1

^a Single patient had atrial fibrillation also had SVT.^b Single patient with atrial fibrillation also had an episode of severe bradycardia.^c Single patient with CHF also had atrial fibrillation.^d One patient with NSTEMI also has atrial fibrillation. PEA, pulseless electrical activity.

TABLE 5.**Binary logistic analysis for predictors of posttransplant cardiac events < 90 days**

Parameters	R	P	OR	95% CI
Age, y	0.025	0.497	1.025	0.955-1.100
Race				
White vs others	-0.241	0.710	0.786	0.220-2.804
AA vs others	0.762	0.267	2.143	0.557-8.238
Hispanic vs others	-20.055	0.999	0.000	0.000
Male sex	-0.079	0.887	0.924	0.309-2.758
Organ type (liver vs liver/kidney)	-0.477	0.473	0.621	0.169-2.281
BMI (≥ 30 vs < 30)	0.350	0.494	1.419	0.520-3.871
DM	0.050	0.923	1.051	0.379-2.917
Lipid profile, mg/dL				
Cholesterol	0.001	0.880	1.001	0.992-1.010
TG	-0.004	0.434	0.996	0.986-1.006
LDL	-0.004	0.553	0.996	0.982-1.010
HDL	0.011	0.381	1.011	0.987-1.035
MELD score at listing	0.029	0.448	1.030	0.955-1.110
Obstructive CAD	-0.199	0.719	0.820	0.278-2.417
Left main	0.141	0.790	1.152	0.407-3.258
LAD (junction of middle and distal one third)	0.114	0.549	1.121	0.771-1.630
LAD (proximal one third of septal branch)	-5.002	1.000	0.007	0.000-
LAD (proximal one third diagonal branch)	-0.060	0.854	0.942	0.499-1.779
Proximal one third of the obtuse marginal branch of the CFX	0.235	0.378	1.264	0.751-2.129
CFX	-0.007	0.984	0.993	0.492-2.003
RCA (up to and the origin of the PDA)	-0.112	0.607	0.894	0.585-1.368
Proximal one third of PDA	0.179	0.668	1.196	0.528-2.710
Combined Reardon score	-0.007	0.843	0.993	0.925-1.066

DM, diabetes mellitus.

all these patients before their LT. All CABG were performed at remote interval from their LT (median, 9 years; range, 2-32 years). In the remaining 7 patients, CAD was mostly confined to circumflex or posterior descending artery (PDA) with up to 50% to 60% stenosis with or without mild left anterior descending (LAD) involvement (up to 50% stenosis) that was considered nonobstructive by the consulting cardiologist and/or had good collateral flow that was considered acceptable to proceed with LT in the setting of a negative stress test. One of these 7 patients had a

subtotally occluded right coronary artery (RCA) with vigorous collaterals from the left coronary system.

Patients with obstructive CAD were older (61.2 ± 6.2 vs 55.7 ± 7.2 , $P = 0.001$), but the prevalence of diabetes mellitus, hypertension, obesity, tobacco use and mean levels of total cholesterol, TG, LDL, and HDL were similar in these groups (Table 2). Calculated MELD score was lower in the obstructive CAD group (15.44 ± 6.58 vs 18.79 ± 18.79 , $P = 0.033$). Frequency of involvement of various coronary segments and severity of involvement based on Reardon

TABLE 6.**Etiology of death in the angiogram and the nonangiogram group**

	Angiogram group (n = 36)		Nonangiogram group I (n = 21)	Nonangiogram group II (n = 32)
Etiology of death	Nonobstructive CAD (n = 22)	Obstructive CAD (n = 14)		
Sepsis	5	4	2	9
CVA	3	0	1	0
Malignancy	1	5	4	5
Respiratory failure	3	0	3	1
Cardiac events	5	2	5	5
Recurrent HCV	1	2	4	0
Trauma	0	0	1	0
Pancreatitis	0	0	1	0
Unknown	4	1	0	9
Renal failure	0	0	0	0
Graft failure	0	0	0	2
Suicide	0	0	0	1

FIGURE 3. Posttransplant survival in recipients with CAD analyzed based on severity of obstruction (A), number of segments involved (B), and extent of disease (C).

score is summarized in Table 3. Of the 29 patients with obstructive CAD, 7 (24.1%) had single vessel disease, and 22 (75.9%) had multivessel disease. The most frequently affected vessels were the junction of middle and distal one-third of the LAD (55.2%), RCA to the origin of the PDA (55.2%), followed by proximal one third of the obtuse marginal branch of the circumflex (CFX) (34.5%) (Table 3). The severity of involvement was assessed by the Reardon severity score (Table 3). The most severely affected coronary arteries were the RCA (1.9 ± 1.6), and the junction of middle and distal one third of the LAD (1.83 ± 1.7), followed by the proximal one third of the obtuse marginal branch of the CFX (0.9 ± 1.31). The mean Reardon severity score was 11.28 ± 8.86 .

Cardiac events within 90 days of LT in the angiogram group and the nonangiogram control group are presented in Table 4. Significant postoperative cardiac events within 90 days of LT were noted in 23 (26.4%) of the 87 LT recipients who underwent angiogram compared to 8 (9.2%) of the 72 patients in the nonangiogram control group I and 6

(5.2%) of the 119 in the nonangiogram control group II ($P < 0.001$) (Table 4). The frequency of cardiac events was not significantly different in the recipients with and without obstructive CAD (8 [27.5%] vs 15 [25.8%], $P = 0.719$). Despite no difference in the overall frequency of cardiac events, 3 of the LT recipients with obstructive CAD sustained myocardial infarction, 2 with non-STEMI (NSTEMI), and 2 with STEMI. However, only 1 LT recipients without obstructive CAD developed NSTMI. Atrial fibrillation was noted in 3 LT recipients with obstructive CAD, and 11 in the group without CAD. The only LT recipient who developed CHF within 90 days of LT, did not have obstructive CAD before LT. Of note, routine posttransplant surveillance ECHO is not performed at our center, hence true prevalence of subclinical CHF may have been underestimated. No specific pre-LT or angiographic variable predicted development of postoperative cardiac events (Table 5).

Thirty-six (41.4%) of the 87 recipients of LT died during follow-up, 7 (8%) died within 90 days of the LT. Three of the 7 patients with early death had CAD ($\geq 50\%$ stenosis).

However, cardiac etiology of death could be attributed to only a single patient, and the remainder died of infectious complications. Etiology of death in the obstructive and nonobstructive CAD groups are summarized in Table 6. Twenty-one (29.2%) of the LT recipients in the nonangiogram control group I, and 32 (26.7%) of the nonangiogram control group II died during the follow-up, and the etiology of these deaths is summarized in Table 6.

Comparable posttransplant survival was noted irrespective of presence or absence of significant CAD (<50% stenosis vs $\geq 50\%$ stenosis) by Kaplan-Meier analysis; although a trend for inferior survival was noted beyond 4 years of follow-up since LT in the obstructive CAD group that was statistically not significant ($P = 0.357$, Figure 3A). Survival analysis based on the number of segments (none, 1-2, > 2 segments) involved ($P = 0.304$, Figure 3B), or based on Reardon severity score (0, 1-9, >10) did not reveal any survival differences although there was trend for inferior survival with higher Reardon score ($P = 0.224$, Figure 3C). Analysis comparing subgroups of LT recipients with angiographically positive CAD (obstructive CAD), angiographically negative (nonobstructive or no CAD), and propensity matched control group with cardiovascular risk profile (control group I), and consecutive patients without any usual major CV-risk profile (control group II) did not show a survival difference ($P = 0.184$, log rank, Figure 4).

We further performed an exploratory analysis to assess demographic and clinical variable associated with survival using Cox Proportional Hazard model (Table 7). On univariate analysis, factors associated with inferior survival included postoperative cardiac events (acute coronary syndrome, arrhythmia, CHF) within 90 days of LT ($P = 0.035$; hazard ratio [HR], 2.116; 95% confidence interval [CI], 1.056-4.238) and obstructive lesion of the CFX artery ($P = 0.028$; HR, 2.892; 95% CI, 1.222-7.456).

Using somewhat liberal entry ($P < 0.1$), we entered Reardon score, HDL level, postoperative cardiac events within 90 days of LT, along with obstructive lesion of the

circumflex artery and LAD (junction of middle and distal one third) as inter-related variable into the multivariate Cox Proportional Hazard model using “enter” method. We noted, postoperative cardiac events within 90 days of LT as a strong predictor of inferior survival after LT ($P = 0.038$; HR, 2.150; 95% CI, 1.042-4.435). This was further evaluated using Kaplan-Meier analysis, and a significantly inferior survival was noted in recipients in the angiogram group who had early postoperative cardiac events ($P = 0.031$, Figure 5A). A trend for inferior survival was noted in the nonangiogram group I with early postoperative cardiac events, although this was statistically not different ($P = 0.376$, Figure 5B), postoperative cardiac events significantly influenced survival in the nonangiogram group II ($P < 0.002$, Figure 5C).

The length of hospital stay (16.16 ± 20.52 vs 13.21 ± 11.55 days, $P = 0.645$) and intensive care unit (ICU) stays (7.58 ± 16.76 vs 8.5 ± 12.6 days, $P = 0.685$) were not significantly different irrespective of the prevascularization severity of CAD in the angiogram study group (<50% stenosis vs $\geq 50\%$ stenosis). The length of hospital stay (15.17 ± 18.02 vs 11.64 ± 12.37 , 11.97 ± 10.17 days, $P = 0.169$) was similar in the 3 groups. The ICU stay (7.88 ± 15.45 vs 5.27 ± 11.22 days, $P = 0.145$) was similar in the angiogram study group compared with the nonangiogram control group I matched for cardiovascular risk profile. However, significantly decreased ICU stay was noted in the nonangiogram control group II which was not matched for cardiovascular risk profile compared with the angiogram group (3.85 ± 3.42 vs 7.88 ± 15.45 days, $P = 0.011$).

DISCUSSION

The main finding of this study is that, in appropriately selected LT recipients with angiographically proven but revascularized CAD, posttransplant survival is independent of the number of vessels with CAD or severity of CAD. We specifically choose a study group to include only those patients who underwent angiography to evaluate for evidence of CAD to avoid the inclusion of patients who were evaluated exclusively with noninvasive CAD testing due to concerns over the lack of reliability of noninvasive CAD screening methods in the LT candidate population.⁹⁻¹⁴ A recent study has also recommended potential benefit of cardiac angiogram in orthotopic LT candidates in improving posttransplant outcome.¹⁵ This group of patients with high risk for CAD who underwent angiogram was further compared with propensity score matched control chosen from the same period without history of having angiogram before their LT. Two control groups were specifically chosen, control group I matched for several of the known risk factors for CAD, such as age (stratified by age groups), sex, stratified MELD score groups, diabetes, hypertension, stratified BMI groups, and history of smoking; and control group II included consecutive patients seen over the same period and not matched for CV risk factors.

The current study explores the relationship of CAD and posttransplant outcome of LT recipients in subjects undergoing preoperative angiography using a severity score (obstructive vs nonobstructive), extent score (using Reardon vessel score), and multiplicity score (number of vessels involved). We have defined obstructive CAD as 50% or greater diameter stenosis based on well-established standards.¹⁶⁻¹⁹ We also

FIGURE 4. Posttransplant survival in LT recipients: angiogram group compared with nonangiogram control group I and II.

TABLE 7.
Cox regression analysis estimating hazards for survival

	Sig.	HR	Univariate analysis	
			95.0% CI for HR	
			Lower	Upper
Age at LT, y	0.717	1.009	0.963	1.056
Race (white vs others)	0.285	0.651	0.297	1.430
Sex (male vs female)	0.309	1.483	0.695	3.166
Listing MELD score	0.722	1.009	0.962	1.058
Organ type (liver vs liver/kidney)	0.447	0.667	0.236	1.891
BMI (≥ 30 vs < 30)	0.673	0.868	0.451	1.672
Diabetes (yes vs no)	0.141	1.637	0.850	3.154
Hypertension	0.163	1.604	0.826	3.113
History of smoking	0.520	1.241	0.643	2.399
Cholesterol, mg/dL	0.963	1.000	0.994	1.006
TG, mg/dL	0.949	1.000	0.994	1.006
LDL, mg/dL	0.503	0.997	0.989	1.005
HDL, mg/dL	0.077	1.014	0.999	1.029
Obstructive CAD	0.358	1.371	0.699	2.687
Left main disease	0.327	2.040	0.490	8.503
LAD (junction of middle and distal one third)	0.051	2.077	0.996	4.332
LAD (proximal one third of septal branch)	0.644	0.049	0.000	-
LAD (proximal one third diagonal branch)	0.663	0.728	0.175	3.034
Proximal one third of the obtuse marginal branch of the CFX	0.291	1.672	0.644	4.340
CFX	0.028	2.892	1.122	7.456
RCA (up to and the origin of the PDA)	0.532	1.286	0.585	2.826
Proximal one third of PDA	0.740	0.714	0.098	5.216
Reardon score	0.082	0.604	0.306	1.193
HCV serologic status (positive vs negative)	0.147	0.710	0.332	1.518
HCC pre-LT (yes vs no)	0.956	0.980	0.470	2.041
Cardiac events within 90 d of LT	0.035	2.116	1.056	4.238
Multivariate analysis				
Reardon score	0.385	1.025	0.970	1.084
Cardiac events within 90 d of LT	0.038	2.150	1.042	4.435
HDL, mg/dL	0.074	1.013	0.999	1.028
CFX and LAD (junction of middle and distal one third) ^a	0.898	1.109	0.228	5.400

^a Considering possible interaction, CFX and LAD (junction of middle and distal one third) were selected together as interrelated variable for multivariate analysis.

recognize that many patients in the nonobstructive CAD may in fact have mild degree of CAD. Nonetheless, previous studies have shown no significant impact on mortality with mild CAD as compared to no CAD, hence categorization of these 2 groups into 1 is justifiable.¹⁷ The mortality rates in LT recipients with CAD described in earlier studies vary considerably.^{2,9,20} In one of the earliest series reported by Plotkin et al, 32 LT recipients with angiographically proven CAD had an overall mortality of 50% over a 1- to 3-year follow-up period, and nearly a third of the deaths occurred within 3 months of LT.²¹ A recent study suggests that although all-cause mortality is not different, CAD-related mortality remains high in the CAD group.²² Our data are in conflict with these results, suggesting that patients with angiographically proven but revascularized CAD can safely undergo LT and have posttransplant survival. Wray et al¹ noted that when current CAD treatment strategies are used before transplant, post-LT survival is not significantly different between patients with and without obstructive CAD. A similar observation was noted in an earlier study, although the study was not designed to assess long-term mortality.¹ Our results are further supported by Skaro et al,²³ who concluded LT

in patients with CAD is not associated with prohibitive risk for cardiac events and patient mortality.

To assess the impact of the degree of severity of CAD, we used a scoring system, Reardon score. The utility of this vessel scoring system has been tested in multiple prior published studies.^{6,24,25} Using this scoring system, we categorized groups into no CAD (vessel score = 0), mild CAD (vessel score = 1-9), and severe CAD (vessel score > 10). We examined posttransplant survival in the LT recipients based on severity of CAD (obstructive vs nonobstructive, Figure 3A), number of vessels involved (Figure 3B), and extent of CAD using Reardon severity score (0, 1-9, > 10, Figure 3C). The difference in survival irrespective of the severity, extent, and number of vessels involved was similar in these LT recipients with angiographically proven but revascularized CAD. When LT recipients compared with a propensity matched control group I with several of the known risk factors for CAD, and a control group II that is not matched for known risk factors for CAD, we observed the angiogram group still had comparable survival ($P = 0.145$). LT recipients with a significant burden of CAD are certainly at risk of progressive CAD after LT secondary to the effects of chronic

FIGURE 5. Posttransplant survival in recipients based on occurrence of early cardiac events in all LT recipients who had angiogram (A), in the control group I without angiogram matched for CV risk factors (B), and control group II not matched for usual CV risk factors (C).

immunosuppression,²⁶⁻²⁹ and longer follow up is clearly needed to better assess the long-term survival outcome.

We noted a significantly increased number of early posttransplant cardiac events in the angiogram study group as compared to the nonangiogram control group, although frequency of cardiac events was not different in the obstructive versus nonobstructive CAD group. We suspect this increased predisposition for early postoperative cardiac events could potentially be related to their underlying CAD, because the matched controls with similar cardiovascular risk factors without suspected CAD at baseline have less early postoperative cardiac events. We were, however, unable to point out any predisposition for such events based on the severity or extent of CAD. In addition, we noted that these early cardiovascular events (<90 days) have potential implication on their posttransplant survival, even in the nonangiogram study group. Our results are supported by recent studies which concluded that LT recipients with early cardiac events have negative survival outcome.^{30,31} Of note, numerically higher serious cardiac events, such as myocardial infarction, were noted in the obstructive CAD group within the first 90 days. It

is a known fact that long-term (>1 year) survival rates after interventions, such as PCI and CABG, are inferior for patients without obstructive CAD.^{17,32,33} An earlier study has reported that cardiovascular events are the third leading cause of late graft loss on long-term follow-up after LT.³⁴

The current study has several limitations. Retrospective review of medical records likely underestimates the true prevalence and severity of CAD as angiography is performed in only select number of high-risk patients undergoing LT. Adherence to the standard operating practice for angiogram has varied over the years driven by urgency for LT, renal dysfunction, coagulopathy, organ failure limiting adequate evaluation of the cardiac status in all LT candidates which is a limitation in this retrospective study. As such, the control group with CV risk factors could have underlying mild nonobstructive CAD that may have been missed as all these cases were not evaluated with angiogram. We have tried to address this issue using 2 control groups, one matched for CV risk factors, and the other control group that was not matched for CV risk factors. The selection criteria of LT recipients with CAD are center-specific and can potentially introduce a bias, which may limit

wider applicability to other centers. However, single center analysis does provide some clarity to certain variables that may not be captured in large registries. The strength of the current study lies in its accurate identification of CAD by coronary angiogram that was reviewed by an independent reviewer, an invasive cardiologist. Preoperative information, such as cardiac symptomatology, noninvasive stress testing results, ventricular function, and exercise tolerance were not evaluated in this study. Additionally, the sample size of the current study is small, and the results of the current study should be interpreted with caution, and needs to be validated in larger prospective studies.

We conclude that listing for LT after appropriate revascularization in the preoperative period in patients deemed high risk for potential or known CAD will lead to comparable post-LT survival compared with those without obstructive CAD irrespective of underlying severity, or extent disease, if appropriately revascularized. As such, severity or extent of CAD, if appropriately treated, should not be an exclusion criterion for undergoing LT. Survival in the LT recipients undergoing angiogram is comparable to those LT recipients who are presumed to have no CAD based on noninvasive tests. Postoperative cardiac events are uniformly associated with inferior survival in LT recipients irrespective of underlying CAD.

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