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Risk Factors and Cardiovascular Events in Orthotopic Liver Transplantation

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ABSTRACT

Background & Aims: Patients undergoing liver transplantation often have significant cardiovascular risk factors and may experience cardiac-related morbidity and mortality. The aim of this study was to assess the frequency of cardiovascular risk factors and outcomes in this population, and to identify factors predictive of post-transplant cardiac morbidity and mortality.

Methods: We studied 261 patients who underwent liver transplantation at a single Veterans' Affairs Medical center between 1997 and 2015 to evaluate new cardiovascular events post-transplantation.

Results: The cohort consisted of 261 patients (253 men and 8 women) with a mean age of 58.3 (± 6.5 years), mean model for end-stage liver disease score of 18.0 (±7.2), and mean Framingham risk score of 8.1 (± 4.9). After a median follow-up of 82 months a total of 75 (28.7%) patients died, with 13 deaths (17.3%) attributed to a primary cardiovascular event and 9 (12%) deaths due to a coronary-specific event. Coronary events and/or the need for revascularization post-transplant occurred in 24 (9.2%) patients. The strongest pre-transplant predictors of mortality were age (p=0.01), Framingham risk score (p=0.01), preexisting coronary artery disease (p=0.01), and preexisting dyslipidemia (p=0.01). The strongest post-transplant predictors of mortality were new-onset hypertension (p=0.01) and new-onset diabetes mellitus (p=0.03) post-transplant.

Conclusions: In this cohort of veterans, coronary artery disease was significantly associated with mortality in the post liver transplantation population; however, the majority of deaths after transplant were attributable to other causes.

Key words: coronary artery disease – cardiovascular disease – risk factors – risk stratification – liver transplantation.

Abbreviations: CABG: coronary artery bypass graft surgery; CAD: coronary artery disease; CPRS: computerized patient record system; CTP Score: Child Turcotte Pugh score; CVA: cerebrovascular accident; DM: diabetes mellitus; HMG CoA reductase inhibitors: hydroxyl methyl glutaryl coenzyme A reductase inhibitors; HBP: high blood pressure; MELD score: model for end-stage liver disease score; MI: myocardial infarction; MPI: myocardial perfusion imaging; OLT: orthotopic liver transplantation; PCI: percutaneous coronary intervention; TIA: transient ischemic attack.

INTRODUCTION

Liver transplantation is the only effective treatment for the reversal of end-stage liver disease. In well selected patients, orthotopic liver transplantation (OLT) is associated with a 10-year survival in excess of 60% [1]. Studies show that a high percentage of patients with chronic liver disease have pre-existing coronary artery disease (CAD) at the time of transplantation, and a history of CAD increases cardiovascular-related mortality in the perioperative and post-transplantation setting. In the past two decades, the mean age at OLT has progressively increased, and currently almost 2/3 of patients receiving transplants are over the age of 50 [2, 3]. This trend has been accompanied by an increase in the number of OLT candidates with pre-existing cardiovascular pathology [4].

Cardiovascular events are an important and potentially preventable cause of death after OLT [5]. The development of new cardiovascular risk factors such as high blood pressure (HBP), diabetes mellitus and hyperlipidemia as a side effect of immunosuppression therapy is common and can exacerbate adverse cardiovascular events.

Organs for liver transplantation are a scarce resource and must be allocated in a manner that maximizes their utility. For this reason, risks that might be acceptable in patients undergoing surgery for other critical indications may be prohibitive when evaluating a patient for OLT [6]. Patients with severe cardiac disease are routinely excluded from transplantation; as a consequence, short-term post-transplant cardiac mortality is low as compared to non-cardiac causes of death [7] and short-term post-transplant cardiac events are mostly related to hemodynamic and electrolyte derangements. However, long-term post-transplant cardiac events related to progressive CAD are a growing concern. Even moderate elevations of blood pressure and dyslipidemia are associated with poorer outcomes [8]. In previous studies, about 20% of long term-post transplant deaths were attributed to cardiac events [9] and this proportion can be expected to increase with the aging of the OLT candidate population.

While guidelines have been proposed [3, 10], there is no consensus as to what constitutes an adequate pre-transplant cardiac evaluation or an acceptable cardiac risk, and data to permit accurate estimation of post-transplant cardiac risk are lacking [11]. Because of these issues [12-14] we retrospectively studied OLT patients at our center to assess the frequency of cardiovascular risk factors and outcomes in this population, and to identify factors predictive of post-transplant cardiac morbidity and mortality.

METHODS

Study Population

After approval by the Institutional Review Board, the Veterans' Administration computerized patient record system (CPRS) was used to investigate patients who underwent OLT in our program between September 1997 and August 2015. All patients who underwent transplantation were included in the study and no patients were excluded. Overall, there were 261 patients who received OLT and for whom data was available for analysis, and thus these individuals met inclusion criteria. Data were obtained for age, gender, ethnicity, height, body weight, body mass index, blood pressure, smoking status, past medical history, diagnostic studies, medications, and post-OLT course until the patients' death or until August 2015, whichever came first. The model for end-stage liver disease (MELD) score [15], Child Turcotte Pugh (CTP) score [16], Framingham risk score [17] were recorded or calculated, and the results of cardiac stress tests and cardiac catheterization were recorded. Coronary artery stenosis 70% or greater on coronary angiogram was considered significant. Comorbidities such as CAD, defined as documented history of CAD, HBP or diabetes mellitus and dyslipidemia were extracted from the patients' history in the electronic chart. The patients' 12-lead electrocardiograms and echocardiography results were also reviewed. We recorded the use of beta blockers and hydroxyl methyl glutaryl coenzyme A (HMG CoA) reductase inhibitors before and after transplantation [18].

Outcomes

Mortality data were collected by a review of Veterans Affairs electronic records and benefits records. New post-transplant cardiovascular events were recorded, including unstable angina, myocardial infarction (MI), percutaneous coronary intervention (PCI) with or without coronary stent placement, coronary artery bypass graft surgery (CABG), cerebrovascular accident, or transient ischemic attack. We categorized major coronary events as MI, unstable angina, PCI, or CABG.

Statistical Analysis

Statistical analyses were conducted using JMP version 8. All statistical tests were two-sided with a significance level of 0.05. Fisher's exact test was used to compare categorical variables. Survival curves for outcomes were prepared with the use of the Kaplan-Meier method and Cox proportional hazards model. The incidences of cardiac events were calculated as simple proportions. Descriptive statistics was used to analyze survival duration and outcomes in candidates who underwent diagnostic studies or interventions.

RESULTS

A total of 261 patients who underwent OLT from September 1997 to August 2015 at our Veterans' Affairs Medical Center were studied for a median follow-up period of 82 months. Consistent with the population served by the Department of Veterans' Affairs Health System, 96.9% were male. The mean age at transplantation of 58.3±6.5 years, and the mean body mass index (BMI) was 28.9±4.5 kg/m^2. The average MELD score 18.0±7.2 and Framingham risk score was 8.1±4.9. In this cohort 241 (92.3%) patients were non-smokers and 39 (14.9%), 89 (34.1%) had preexisting HBP, 69 (26.4%) had preexisting diabetes mellitus, 41 (15.7%) had preexisting dyslipidemia, and 39 (14.9%) had preexisting CAD prior to OLT (Table I).

A total of 75 patients (28.7%) died of all causes after OLT. Post-OLT new major cardiovascular events occurred in 37 patients (14.2%), of whom 13 died (35%, comprising 17.3% of all deaths). There were 24 patients with new major coronary events post-OLT (9.2%), and among those there were 9 deaths (p=0.34). Of the 39 total patients with pre-existing CAD, 15 (38.4%) died in the post-OLT follow-up period. Patients with pre-existing CAD had lower rates of both major coronary events and cardiovascular events, although not statistically significant (p=0.06 and p=0.13, respectively). Age had no impact on risk of death, major coronary events or new cardiovascular events. Non-smoker status was associated with fewer major coronary events post-OLT and was suggestive of a reduced risk of death and new cardiovascular events (see Table I-III).

Absence of a reversible defect on pre-transplant stress myocardial perfusion imaging (MPI) was associated with a significantly lower risk for death (p=0.001) and major coronary events (p=0.03) in a post-OLT setting and approached significance for reduced risk of new cardiovascular events or intervention (p=0.055). Meanwhile reversible defect on MPI demonstrated a significantly decreased risk for mortality (p=0.002) and major coronary events (p=0.05) post-OLT and suggested a decreased risk for new cardiovascular events (p=0.08).

The absence of CAD on pre-transplant cardiac catheterization was associated with significantly fewer new cardiovascular events (p=0.007) and was suggestive of less all-cause mortality and major coronary events although these did not reach statistical significance (p=0.6 and p=0.12, respectively).

Table I. Post liver transplant clinical characteristics and all-cause mortality

Variables	Patients N=261	Dead N=75	Alive N=186	p
Age	58.3 ± 6.5	59.1 ± 7.2	57.9 ± 6.2	0.20
Male, n (%)	253 (96.9)	73 (97.3)	180 (96.8)	0.81
Caucasian, n (%)	169 (64.8)	50 (66.7)	119 (64.0)	0.77
Body mass index	28.9 ± 4.5	28.5 ± 4.5	29.0 ± 4.5	0.49
Non-smokers, n (%)	241 (92.3)	66 (88)	175 (94.1)	0.12
MELD score	18.0 ± 7.2	18.1 ± 7.9	17.9 ± 6.9	0.89
CTP score	9.6 ± 2.3	9.6 ± 2.3	9.6 ± 2.3	0.86
Serum creatinine	1.3 ± 0.9	1.3 ± 0.8	1.3 ± 1.0	0.69
Framingham risk score	8.1 ± 4.9	8.7 ± 5.4	7.8 ± 4.7	0.28
Pre-OLT CAD, n (%)	39 (14.9)	15 (20.0)	24 (12.9)	0.1
Pre-OLT HBP, n (%)	89 (34.1)	26 (34.7)	63 (33.9)	0.90
Pre-OLT dyslipidemia, n (%)	41 (15.7)	9 (12)	32 (17.2)	0.35
Pre-OLT diabetes mellitus, n (%)	69 (26.4)	22 (29.3)	47 (25.3)	0.53
Post-OLT CVA/TIA, n (%)	16 (6.1)	6 (8)	10 (5.4)	0.40
Post-OLT new HBP, n (%)	105 (40.2)	25 (33.3)	80 (43.0)	0.16
Post-OLT new dyslipidemia, n (%)	96 (36.8)	31 (41.3)	65 (34.9)	0.39
Post-OLT new diabetes mellitus, n (%)	58 (22.2)	13 (17.3)	45 (24.2)	0.25
Post-OLT acute graft rejection, n (%)	48 (18.4)	14 (18.7)	34 (18.3)	0.94
Post-OLT coronary events and/or coronary Interventions, n (%)	24 (9.2)	9 (12)	15 (8.1)	0.34
Post-OLT cardiovascular events, n (%)	37 (14.2)	13 (17.3)	24 (12.9)	0.43
Pre-OLT beta blockers, n (%)	147 (56.3)	41 (54.7)	106 (57)	0.78
Post-OLT beta blockers, n (%)	132 (50.6)	40 (53.3)	92 (49.5)	0.58
Post-OLT HMG CoA reductase inhibitors, n (%)	50 (19.2)	12 (16)	38 (20.4)	0.48
Pre-OLT reversible defect on MPI, n (%)	69 (26.4)	12 (16)	57 (30.6)	0.002
Pre-OLT no defect on MPI, n (%)	94 (36)	40 (53.3)	54 (29)	0.001
Pre-OLT no CAD on cardiac catheterization, n (%)	95 (36.4)	25 (33.3)	70 (37.6)	0.60

CAD: coronary artery disease; CTP score: Child Turcotte Pugh score; CVA: cerebrovascular accident; HMG CoA reductase inhibitors: hydroxyl methyl glutaryl coenzyme A reductase inhibitors; HBP: high blood pressure; MELD score: model for end-stage liver disease score; MPI: myocardial perfusion imaging; OLT: orthotopic liver transplantation; TIA: transient ischemic attack.

Existence of pre-transplant HBP, diabetes mellitus or dyslipidemia was not associated with significantly higher risks of death, major coronary events or new major cardiovascular events post-transplant. New-onset HBP developed in 105 (40.2%) of patients post-OLT, with new-onset diabetes mellitus in 58 (22.2%), and new-onset dyslipidemia developing in 96 patients (36.8%).

Post-transplantation use of beta blockers was associated with fewer major coronary events (p=0.05), but not related to a significantly lower risk of death or new major cardiovascular events p=0.001). HMG CoA reductase inhibitor use post-OLT showed a reduced chance of developing major coronary events (p=0.001) and new major cardiovascular events (p=0.001).

Pre-existing CAD was associated with significantly worse outcomes compared to no pre-existing CAD (Fig. 1). The logistic regression model with the binary outcomes of post-OLT major coronary events or new cardiovascular events versus no event did not return any statistically significant predictors. Time to death is the only time-to-event outcome in the analysis and was censored at 10 years. When time effect was

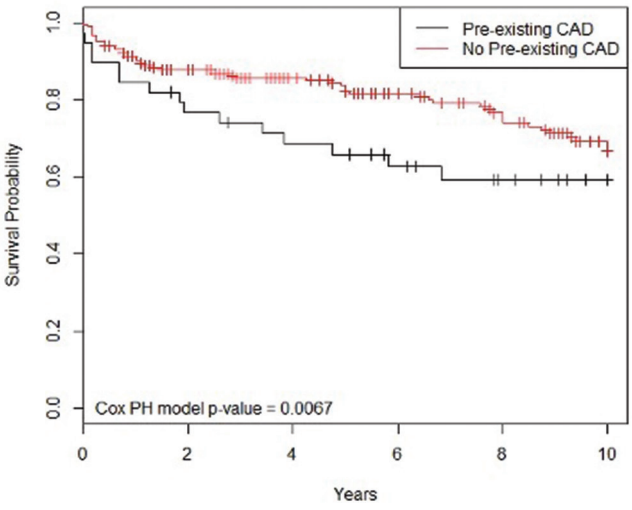

Fig. 1. Mortality after liver transplant in patients with pre-existing coronary artery disease versus patients without pre-existing coronary artery disease.

Table II. Post orthotopic liver transplant major coronary events

Variables	Total patients N=261	Post OLT major coronary events N=24	No post OLT major coronary events N=237	p
Age	58.3 ± 6.5	59.0 ± 7.1	58.2 ± 6.5	0.61
Male, n (%)	253 (96.9)	24 (100)	229 (96.6)	0.76
Caucasian, n (%)	169 (64.8)	18 (75)	151 (63.7)	0.37
Body mass index	28.9 ± 4.5	29.0 ± 5.2	28.8 ± 4.5	0.92
Non-smokers, n (%)	241 (92.3)	19 (79.2)	222 (93.7)	0.02
MELD score	18.0 ± 7.2	18.2 ± 8.4	18.0 ± 7.1	0.92
CTP score	9.6 ± 2.3	9.7 ± 2.5	9.6 ± 2.3	0.83
Serum creatinine	1.3 ± 0.9	1.4 ± 0.9	1.3 ± 1.0	0.70
Framingham risk score	8.1 ± 4.9	9.2 ± 5.3	8.0 ± 4.9	0.38
Pre-OLT CAD, n (%)	39 (14.9)	7 (29.2)	32 (13.5)	0.06
Pre-OLT HBP, n (%)	89 (34.1)	8 (33.3)	81 (34.2)	0.95
Pre-OLT dyslipidemia, n (%)	41 (15.7)	2 (8.3)	39 (16.5)	0.38
Pre-OLT diabetes mellitus, n (%)	69 (26.4)	9 (37.5)	60 (25.3)	0.22
Post-OLT CVA / TIA, n (%)	16 (6.1)	3 (12.5)	13 (5.5)	0.17
Post-OLT new HBP, n (%)	105 (40.2)	11 (45.8)	94 (39.7)	0.66
Post-OLT new dyslipidemia, n (%)	96 (36.8)	14 (58.3)	82 (34.6)	0.02
Post-OLT new diabetes mellitus, n (%)	58 (22.2)	9 (37.5)	49 (20.7)	0.07
Post-OLT acute graft rejection, n (%)	48 (18.4)	5 (20.8)	43 (18.1)	0.78
Pre-OLT beta blockers, n (%)	147 (56.3)	12 (50)	135 (57)	0.52
Post-OLT beta blockers, n (%)	132 (50.6)	17 (70.8)	115 (48.5)	0.05
Post-OLT HMG CoA reductase inhibitors, n (%)	50 (19.2)	13 (54.2)	37 (15.6)	0.001
Pre-OLT reversible defect on MPI, n (%)	69 (26.4)	2 (8.3)	67 (28.3)	0.05
Pre-OLT no defect on MPI, n (%)	94 (36)	12 (50)	82 (34.6)	0.03
Pre-OLT no CAD on cardiac catheterization, n (%)	95 (36.4)	5 (20.8)	90 (38)	0.12

For abbreviations see Table I.

ignored and using a binary logistic regression model with the outcome being all-cause death versus alive, the Framingham risk score (p=0.02), preexisting coronary artery disease (p=0.01), and preexisting dyslipidemia (p=0.01) were the statistically significant predictors. When the time effect (time to death as the outcome) was incorporated, the Cox proportional hazard model was fitted with the covariates presented in Table I. The Cox proportional hazard model identified age (p=0.01), the Framingham risk score (p=0.01), preexisting coronary artery disease (p=0.01), preexisting dyslipidemia (p=0.01), post-OLT new HBP (p=0.01), and post-OLT new diabetes mellitus (p=0.03) as statistically significant predictors of death.

DISCUSSION

The main finding of this analysis is that cardiovascular events were relatively uncommon after transplantation in this cohort of veterans, less than the 20% event rate reported in other studies [19, 20]. Coronary events and/or revascularization procedures post-transplant were also relatively rare in our patients, with no statistically significant increase in mortality. The presence of preexisting CAD prior to transplantation had a statistically significant association with increased post-transplantation mortality. This is consistent with published literature [21-23] and occurred despite conservative listing practices at our hospital in which patients with significant coronary lesions routinely undergo revascularization prior to listing, and those with advanced cardiac disease not amenable to revascularization are not offered transplantation. Though protocols differ across structured liver transplant programs, selection biases occur in all transplant populations and must be considered in interpreting survival data.

Our data suggests that the strongest pre-transplant predictors of mortality are age, Framingham risk score, preexisting coronary artery disease, and preexisting dyslipidemia. We also found that the strongest post-transplant predictors of mortality are post-transplant new onset HBP, and post-transplant new onset diabetes mellitus. We noticed that there was no significant difference in the prescription of beta blockers before and after transplantation. Although pre- and post-transplant use of beta blockers conferred no statistically significant difference in mortality or development of new cardiovascular events, we did find a significant reduction in the risk of major coronary events for patients taking beta blockers post. There was no significant mortality benefit post-transplantation in patients on HMG CoA reductase inhibitors, but there was a statistically significant benefit in the reduction of cardiovascular events and major coronary events. In the non-transplant setting, use of beta blockers and HMG CoA reductase inhibitors to control cardiac risk factors has been demonstrated to reduce mortality,

Table III. Post orthotopic liver transplant new major cardiovascular events

Variables	Total Patients N=261	Post OLT cardiovascular events N=37	No post OLT cardiovascular events N=224	p
Age	58.3 ± 6.5	58.9 ± 6.5	58.2 ± 6.5	0.49
Male, n (%)	253 (96.9)	37 (100)	216 (96.4)	0.60
Caucasian, n (%)	169 (64.8)	29 (78.4)	140 (62.5)	0.06
Body mass index	28.9 ± 4.5	28.7 ± 4.6	28.9 ± 4.5	0.89
Non-smoker, n (%)	241 (92.3)	32 (86.5)	209 (93.3)	0.17
MELD score	18.0 ± 7.2	18.5 ± 8.0	17.9 ± 7.1	0.71
CTP score	9.6 ± 2.3	9.8 ± 2.3	9.6 ± 2.3	0.65
Serum creatinine	1.3 ± 0.9	1.3 ± 0.8	1.3 ± 1.0	0.72
Framingham risk score	8.1 ± 4.9	8.9 ± 5.4	8.0 ± 4.9	0.40
Pre-OLT CAD, n (%)	39 (14.9)	9 (24.3)	30 (13.4)	0.13
Pre-OLT HBP, n (%)	89 (34.1)	11 (29.7)	78 (34.8)	0.58
Pre-OLT dyslipidemia, n (%)	41 (15.7)	3 (8.1)	38 (17)	0.22
Pre-OLT diabetes mellitus, n (%)	69 (26.4)	13 (35.1)	56 (25)	0.22
Post-OLT new HBP, n (%)	105 (40.2)	18 (48.6)	87 (38.8)	0.28
Post-OLT new dyslipidemia, n (%)	96 (36.8)	22 (59.5)	74 (33)	0.003
Post-OLT new diabetes mellitus, n (%)	58 (22.2)	10 (27.0)	48 (21.4)	0.52
Post-OLT acute graft rejection, n (%)	48 (18.4)	7 (18.9)	41 (18.3)	0.92
Pre-OLT beta blockers, n (%)	147 (56.3)	17 (45.9)	130 (58)	0.21
Post-OLT beta blockers, n (%)	132 (50.6)	22 (59.5)	110 (49.1)	0.28
Post-OLT HMG CoA reductase inhibitors, n (%)	50 (19.2)	15 (40.5)	35 (15.6)	0.001
Pre-OLT reversible defect on MPI, n (%)	69 (26.4)	4 (10.8)	65 (29)	0.08
Pre-OLT no defect on MPI, n (%)	94 (36)	15 (40.5)	79 (35.3)	0.055
Pre-OLT no CAD on cardiac catheterization, n (%)	95 (36.4)	7 (18.9)	88 (39.3)	0.007

For abbreviations see Table I.

and while not significant there appears to be a similar trend with these agents in the post-OLT population.

After OLT we found an increased prevalence of HBP and hypercholesterolemia, likely attributable to underutilization of statins in this population [24], and in part, to the use of immunosuppressive medications. There has been increased awareness of new onset diabetes mellitus after a transplant which may be accelerated by immunosuppressant therapy. Interestingly, the development of these post-transplantation risk factors did not appear to significantly increase the likelihood of cardiovascular events and mortality. This is unexpected given the association of these risk factors with ischemic heart disease in many previous studies. [13, 19, 22, 25] However, as more survivors enter their second and third post-transplant decades, the effects of these risk factors may become more apparent.

Although our program has consistently required smoking cessation as a condition for listing, tobacco addiction has proven to be a challenge with a post-transplant relapse in 7.7% of patients. In patients with cardiovascular disease who had achieved durable smoking cessation prior to transplant referral, the long-term cardiac risk was low. This suggests that transplantation of patients with cardiovascular disease can be undertaken with good results provided that long-term control of cardiac risk factors is achieved in the perioperative period: improved control of pre-transplant dyslipidemia, post transplantation HBP, and post transplantation diabetes mellitus.

Our data appears to suggest a higher likelihood of survival both among patients with a reversible defect on pre-transplant MPI, and those without a reversible defect on pre-transplant MPI. This finding may seem paradoxical, but may suggest that patients with a reversible defect on MPI were more likely to undergo subsequent catheterization and achieve definitive diagnosis and appropriate therapy, although this could not be correlated in our dataset. There was a trend towards a reduced mortality risk in patients who had no evidence of CAD on pre-transplant catheterization, although this finding was not significant.

A recent large multicenter study [26] reported that pre-transplant cardiovascular disease was not predictive of post-transplant mortality. That study was specifically designed to examine early mortality, with duration of follow-up limited to three years. The overall low mortality among patients with cardiac disease in that study reflected conservative selection criteria aimed at minimizing operative risk; most of the patients with advanced cardiovascular disease (defined as coronary narrowing > 70% and/or history of revascularization) and a significant proportion of those with asymptomatic noncritical coronary lesions (50-70% stenosis) underwent coronary interventions prior to transplantation. Although differences did not achieve statistical significance, there was a trend at

3 years toward higher mortality in those patients with more advanced pre-transplant cardiac disease. In a study by Skaro et al. [27], of patients who underwent OLT, CAD severity was not found to be a prohibitive contraindication to OLT provided optimal management was provided per guidelines. However, a higher cardiovascular risk index was significantly associated with mortality in their cohort [27]. Our data cannot rule out that, with a longer duration of follow-up, cardiac disease may assume an increasing importance as a cause of mortality, especially in patients with new post-transplantation HBP or diabetes mellitus, and pre-transplantation dyslipidemia requiring treatment with beta blockers, HMG CoA reductase inhibitors, and anti-glycemic agents.

The American Heart Association and European Society of Cardiology have outlined guidelines for evaluation of patients undergoing major surgery [18, 28] but have only recently taken a position on cardiac evaluation specifically for OLT [3, 29]. The transplant guidelines are reasonable but lack strong evidence basis and focus mainly on perioperative and early postoperative cardiac risk. Multiple predictive algorithms have been proposed based on risk factors, yet a high proportion of patients still meet criteria for screening tests and the choice of testing modality is unclear. Newer noninvasive testing modalities have been proposed; however, adequate data supporting their use in this population is insufficient at this time. There is strong supportive evidence that preoperative angiographically significant coronary lesions are associated with worse outcomes after OLT; however, robust prospective studies are required to understand the effect of and best approach to revascularization. In an era of worsening organ shortages, the long-term outcome of transplantation is arguably as important as the short term when selecting transplant candidates, and our ability to predict long term cardiac complications remains limited.

CONCLUSIONS

Our findings support the conclusion that OLT can be carried out with acceptable results in patients with CAD. A demonstrated obligation to long-term patient and physician commitment to mitigate pre-transplantation and post-transplantation cardiovascular risk factors may reasonably be considered in accepting or excluding patients from OLT.

Conflicts of interest: None to declare.

Authors' contributions: A.A., R.D., P.D., H.G., M.F., D.H., and S.P. conceived and designed the study. A.A. collected the data. A.A., B.M. R.D., S.P., M.F., and T.H. interpreted the results. L.K. performed the statistical analysis. A.A. and B.M. analyzed the data and drafted the manuscript. I.J. served as senior author and contributed to each portion of manuscript creation. All authors critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

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