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Liver Transplantation Outcome in Patients with Angiographically-Proven Coronary Artery Disease: A Multi-Institutional Study

A thesis submitted in partial satisfaction

of the requirements of the degree Master of Science

in Clinical Research

by

Randolph Herbert Steadman

2012

ABSTRACT OF THE THESIS

Liver Transplantation Outcome in Patients with Angiographically-Proven Coronary Artery Disease: A Multi-Institutional Study

by

Randolph Herbert Steadman

Master of Science in Clinical Research

University of California, Los Angeles, 2012

Professor Robert M. Elashoff, Chair

The impact of coronary artery disease (CAD) on survival after liver transplantation (LT) is poorly defined. This retrospective cohort study identified adult LT recipients who underwent pre-LT coronary angiography at seven institutions over a 12-year period. Obstructive CAD (≥50% stenosis) was present in 151 of 630 patients, the CAD(+) group. The remaining 479 patients comprised the CAD(-) group. Patient survival was similar for the CAD(+) group (adjusted HR 1.13, CI=[0.79, 1.62], p=0.49) compared to the CAD(-) group after a median follow-up of 24.5 months. The CAD(+) patients were further stratified into severe (CADsev, >70% stenosis, n=96), and moderate CAD (CADmod, 50-70% stenosis, n=55) groups. Survival for the CADsev (adjusted HR=1.26, CI=[0.83, 1.91], p=0.28) and CADmod (adjusted HR=0.93, CI=[0.52, 1.66], p=0.80) groups were similar to the CAD(-) group. With current CAD treatment strategies, post-LT survival is not significantly different between patients with and without angiographic evidence of obstructive CAD.

The thesis of Randolph Herbert Steadman is approved.

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Robert M. Elashoff, Committee Chair

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2012

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BODY OF TEXT

Chapter 1 - Background

Coronary Artery Disease and Liver Transplantation

Effects of Liver Disease on the Cardiovascular System

Impairment in liver function was first associated with the cardiovascular system over 50 years ago with the first description of a hyperdynamic circulation in cirrhotic patients.[1] The authors attributed the condition to an increase in cardiac output and a decrease in peripheral vascular resistance. Today, that attribution remains accurate and the term hyperdynamic is still used, though some have suggested that the term “progressive vasodilatory syndrome” better describes the condition.[2] In the 1990s the molecule nitric oxide was identified as having a central role in the vasodilatory state associated with cirrhosis.[3] In addition the vasodilatory state has been recognized as central to the pathophysiological changes seen in cirrhosis, not only in the cardiovascular system but also in other organ systems. Dilation in regional vascular beds precedes compensatory mechanisms such as sodium and water retention that are designed to expand the plasma volume. The result is a high cardiac output state. Eventually the heart’s ability to compensate is overcome, and cardiac insufficiency ensues. Initially insufficiency is manifested only under stress, such as during exercise or surgery. Under these circumstances increases in left ventricular end-diastolic pressure (LVEDP) lead to subnormal increases in left ventricular ejection fraction (LVEF), which indicates a reduction in left ventricular reserve.[4] The blunted LVEF response to increased LVEDP reflects systolic dysfunction. In addition, diastolic dysfunction has been described, though the clinical significance is less clear.[5]

Effects of Cardiovascular Disease on Liver Transplant Outcomes

Cardiovascular disease is recognized as one of the leading causes of post- transplant mortality after liver transplantation (LT). Reports from the 1990s suggested a 3-year post-transplant mortality as high as 50% in the presence of coronary artery disease (CAD).[6] In a more recent study, the relative risk of post-transplant cardiovascular death was 2.6 compared to an age-matched population without end-stage liver disease (ESLD), despite the exclusion of LT patients with overt cardiovascular disease.[7] In long-term LT survivors, cardiovascular complications and malignancy combined to account for more than 50% of late (>3 years post-LT) mortality.[8] Other authors have reported similar results within the first 6 months post-LT, with cardiac complications accounting for 25% of deaths.[9]

Prevalence of Coronary Artery Disease in Liver Transplant Candidates

The proportion of liver transplant recipients over the age of fifty has increased to 70%, from approximately 45% ten years' ago. The proportion of recipients over the age of 65 has doubled over the last ten years.[10] Meanwhile, the incidence of diabetes has increased to 21 percent of recipients in 2008 (from 15 percent in 1999), and renal insufficiency (creatinine $\geq$ 1.5 mg/dL) rose to 30 percent. Against this backdrop of increasing age and co-morbidities, the prevalence of coronary artery disease is significant, as high as 26% in selected series. [11]

Diagnostic Testing

While an evaluation for the presence of coronary artery disease is indicated, there is no clear consensus on appropriate testing in patients with ESLD. Decreased muscle mass, encephalopathy, ascites, infection, medication use and hospitalization status can limit the usefulness of exercise testing. In one study of patients with an average MELD (Model for End-

stage Liver Disease, an acuity score used to prioritize patients for organ allocation) score of 12, less than 50% of patients were able to participate in treadmill testing.[12]

The most recent American College of Cardiology / American Heart Association (ACC/AHA) guidelines for pre-operative testing for CAD recommends noninvasive testing in patients with an unknown functional capacity who are undergoing vascular (or intermediate risk surgery) *if* the results will change management.[13] However, a number of authors with expertise in liver transplantation designate liver transplant surgery as high risk, and consider noninvasive testing unreliable in the presence of liver disease (described in detail below).[14] Accordingly some have recommended proceeding directly to coronary angiography in the presence of an unknown functional capacity and coronary risk factors.[14,15] Heart rate control with beta blockade, as recommended in the ACC/AHA guidelines, is common in patients with ESLD to control portal hypertension. While this treatment may inadvertently reduce the risk of ischemic complications, it also limits the usefulness of noninvasive testing since it decreases the maximum heart rate response during noninvasive testing. This is responsible for the reduced reliability of noninvasive testing in many patients with ESLD. Additionally, the reduced systemic vascular resistance and increased myocardial contractility seen in patients with ESLD renders the pharmacological maneuvers undertaken during noninvasive testing less effective than in patients without ESLD.

Noninvasive Testing: Echocardiography

In a 1996 study 165 liver transplant candidates were evaluated with dobutamine stress echocardiography (DSE) during cardiac screening. Patients with inducible ischemia (n=9) and a high suspicion of ischemia (n=9) had coronary angiography. Based upon the 18 pts who underwent angiography, the positive predictive value (PPV) of DSE was 33%, and the negative

predictive value (NPV) 89%.[16] This suggests that a negative test is reassuring; the patient is unlikely to have disease. In a study from Northwestern University angiography and DSE were performed in 78 liver transplant candidates. The NPV was 64%, a less reassuring finding than the previous study. The PPV was 44%, again suggesting that positive DSE results were more likely to be falsely positive than representative of CAD. These findings question the value of DSE as a screening tool.[17] Chronotrophic incompetence, associated with lower systolic blood pressures, may limit the effectiveness of dobutamine in achieving the target heart rate.[18] Beta-blockers, commonly used in this population, also limit the ability to achieve the target heart rate, and further decrease the usefulness of DSE in ESLD patients.

Noninvasive Testing: Nuclear Scans

In 93 liver transplant candidates without known CAD who underwent both myocardial perfusion scanning (MPS) and coronary angiography, MPS had a 85% false positive rate in patients with reversible perfusion defects, and a 15% positive predictive value. However, MPS was 100% sensitive (100% negative predictive value).[19] In another study of 83 patients who had SPECT (single-photon emission computed tomography) and coronary angiography, the sensitivity of SPECT was 37% and the specificity was 63% (PPV 47%; NPV 80%). The authors speculated that the poor sensitivity was related to the poor response of end-stage liver disease patients to adenosine and dipyridamole, the vasodilators used in the study.[15]

Left heart catheterization (LHC)

In 1995 coronary angiography was used to assess the prevalence of CAD in liver transplant candidates over the age of 50 with several cardiac risk factors. After excluding patients with angina, MI or coronary revascularization, 13% were found to have moderate or severe stenosis, defined as >30% and >70% stenosis respectively.[20] Given the lack of sensitivity and specificity

of non-invasive tests, some authors have suggested proceeding directly to coronary angiography in high risk patients.[14] Coronary angiography appears to be safe despite the coagulopathy common in this patient population, especially if undertaken via the transradial approach. Others reserve coronary angiography for patients with equivocal or positive non-invasive test results. Institutional biases regarding the role of coronary angiography lead to ethical concerns about randomizing patients to LHC or noninvasive testing. These concerns make it unlikely that a randomized trial of LHC will be performed.

Coronary Revascularization

Few data address coronary revascularization in patients with ESLD. In a series of 13 coronary artery bypass graft surgeries in patients with Child's class A and B cirrhosis the mortality was 31%, compared to <2% in historical controls.[21] In a series of 16 liver transplant candidates, percutaneous coronary intervention (PCI) was 94% successful. Fifteen patients had bare metal stents, while one patient had balloon angioplasty alone. Three of these patients subsequently underwent liver transplantation.[22] PCI appears to be an effective treatment strategy for revascularization in ESLD patients; however, it is unclear if this strategy improves survival compared to medical management.

Controversy exists in this group of patients concerning whether benefits exist in pre-operative coronary artery revascularization in asymptomatic patients. While no trials have been performed in patients prior to liver transplant surgery, a randomized trial of 5800 patients prior to vascular surgery showed no benefit of coronary revascularization prior to surgery.[23] However, a retrospective study suggests a benefit to revascularization prior to abdominal, vascular, thoracic, and head and neck surgery but not urologic, orthopedic, breast, or skin surgery.[24] As a

result of this controversy, considerable variability exists in the screening and management of patients prior to liver transplantation.

After evaluating numerous trials that concentrate on patients undergoing vascular surgery, the ACC/AHA guidelines recommend pre-operative revascularization in patients with 1) stable angina and left main disease, 2) stable angina and 3-vessel disease, 3) stable angina and 2-vessel disease with proximal left anterior descending stenosis, 4) unstable angina and 5) acute ST-elevation MI. Although the recommendations are not specifically directed toward ESLD patients, the ACC/AHA guidelines conclude: “the usefulness of preoperative coronary revascularization is not well-established in high-risk ischemic patients.”

Conclusion

No consensus exists on appropriate cardiac screening prior to liver transplantation. Transplant programs select screening algorithms that take their patients, and outcomes, into account. Since patient populations (age, co-existing disease and cardiac risk factors) vary between programs, as does the programs’ access to the expertise needed for screening tests, this approach is likely to continue until more evidence emerges.

The study that follows is designed to assess the post-LT risk encountered by patients with coronary disease. It describes the effect of angiographically-proven coronary disease on post-LT mortality, and compares the post-LT mortality in the CAD positive group with the post-LT mortality in the CAD negative group.

References

1. Kowalski HJ, Abelmann WH. The cardiac output at rest in Laennec's cirrhosis. *J Clin Invest.* Oct 1953;32(10):1025-1033.

2. Iwakiri Y, Groszmann RJ. The hyperdynamic circulation of chronic liver diseases: from the patient to the molecule. *Hepatology.* Feb 2006;43(2 Suppl 1):S121-131.

3. Groszmann RJ. Hyperdynamic circulation of liver disease 40 years later: pathophysiology and clinical consequences. *Hepatology.* Nov 1994;20(5):1359-1363.

4. Wong F, Girgrah N, Graba J, Allidina Y, Liu P, Blendis L. The cardiac response to exercise in cirrhosis. *Gut.* Aug 2001;49(2):268-275.

5. Moller S, Henriksen JH. Cardiovascular dysfunction in cirrhosis. Pathophysiological evidence of a cirrhotic cardiomyopathy. *Scand J Gastroenterol.* Aug 2001;36(8):785-794.

6. Plotkin JS, Scott VL, Pinna A, Dobsch BP, De Wolf AM, Kang Y. Morbidity and mortality in patients with coronary artery disease undergoing orthotopic liver transplantation. *Liver Transpl Surg.* Nov 1996;2(6):426-430.

7. Johnston SD, Morris JK, Cramb R, Gunson BK, Neuberger J. Cardiovascular morbidity and mortality after orthotopic liver transplantation. *Transplantation.* Mar 27 2002;73(6):901-906.

8. Pruthi J, Medkiff KA, Esrason KT, et al. Analysis of causes of death in liver transplant recipients who survived more than 3 years. *Liver Transplant.* Sep 2001;7(9):811-815.

9. Fouad TR, Abdel-Razek WM, Burak KW, Bain VG, Lee SS. Prediction of cardiac complications after liver transplantation. *Transplantation.* Mar 15 2009;87(5):763-770.

10. HHS/HRSA/HSB/DOT. 2009 OPTN/SRTR Annual Report 1999-20082009.

11. Tiukinhoy-Laing SD, Rossi JS, Bayram M, et al. Cardiac hemodynamic and coronary angiographic characteristics of patients being evaluated for liver transplantation. *Am J Cardiol.* Jul 15 2006;98(2):178-181.

12. Oprea-Lager DE, Sorgdrager BJ, Jukema JW, et al. Clinical value of myocardial perfusion scintigraphy as a screening tool in liver transplant candidates. *Liver Transpl.* Mar 2011;17(3):261-269.

13. Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery): developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *Circulation.* Oct 23 2007;116(17):e418-499.

14. Ehtisham J, Altieri M, Salame E, Saloux E, Ollivier I, Hamon M. Coronary artery disease in orthotopic liver transplantation: pretransplant assessment and management. *Liver Transpl.* May 2010;16(5):550-557.

15. Davidson CJ, Gheorghiade M, Flaherty JD, et al. Predictive value of stress myocardial perfusion imaging in liver transplant candidates. *Am J Cardiol.* Feb 1 2002;89(3):359-360.

16. Donovan CL, Marcovitz PA, Punch JD, et al. Two-dimensional and dobutamine stress echocardiography in the preoperative assessment of patients with end-stage liver disease prior to orthotopic liver transplantation. *Transplantation.* Apr 27 1996;61(8):1180-1188.

17. Harinstein ME, Flaherty JD, Ansari AH, et al. Predictive value of dobutamine stress echocardiography for coronary artery disease detection in liver transplant candidates. *Am J Transplant.* Jul 2008;8(7):1523-1528.

18. Elhendy A, van Domburg RT, Bax JJ, et al. The functional significance of chronotropic incompetence during dobutamine stress test. *Heart.* Apr 1999;81(4):398-403.

19. Aydinalp A, Bal U, Atar I, et al. Value of stress myocardial perfusion scanning in diagnosis of severe coronary artery disease in liver transplantation candidates. *Transplant Proc.* Nov 2009;41(9):3757-3760.

20. Carey WD, Dumot JA, Pimentel RR, et al. The prevalence of coronary artery disease in liver transplant candidates over age 50. *Transplantation.* Mar 27 1995;59(6):859-864.

21. Klemperer JD, Ko W, Krieger KH, et al. Cardiac operations in patients with cirrhosis. *Ann Thorac Surg.* Jan 1998;65(1):85-87.

22. Azarbal B, Poommipanit P, Arbit B, et al. Feasibility and safety of percutaneous coronary intervention in patients with end-stage liver disease referred for liver transplantation. *Liver Transpl.* Jul 2011;17(7):809-813.

23. McFalls EO, Ward HB, Moritz TE, et al. Coronary-artery revascularization before elective major vascular surgery. *N Engl J Med.* Dec 30 2004;351(27):2795-2804.

24. Eagle KA, Rihal CS, Mickel MC, Holmes DR, Foster ED, Gersh BJ. Cardiac risk of noncardiac surgery: influence of coronary disease and type of surgery in 3368 operations. CASS Investigators and University of Michigan Heart Care Program. Coronary Artery Surgery Study. *Circulation.* Sep 16 1997;96(6):1882-1887.

Chapter 2 – Thesis Body

Liver transplantation outcome in patients with angiographically-proven coronary artery disease: a multi-institutional study

Introduction

Recent studies have demonstrated a prevalence of CAD in LT candidates as high, or higher, than in the general population.[1-3] Despite the increased prevalence of CAD in LT candidates, there are few studies that have characterized the effect of CAD severity and treatment on the outcome of LT patients.[4-7] Due to the aging of LT candidates, coronary angiography is increasingly advocated to evaluate LT candidates.[8, 9] Angiography is often employed in place of noninvasive testing in the evaluation of older and higher risk candidates, as noninvasive tests for myocardial ischemia have varying degrees of reliability in LT candidates.[5, 10-14] To date, no multicenter study has investigated the post-LT survival of patients with angiographically-proven obstructive CAD.

We report the results of our analysis of 630 patients who underwent angiography prior to LT at seven U.S. institutions over a 12 year period ending in December 2010. Our primary aim is to characterize post-LT survival in patients with angiographically-proven obstructive CAD compared to patients without angiographic evidence of obstructive CAD. Our secondary aim is to identify the effects of CAD severity on post-LT survival. Based on preliminary single center data, we hypothesized that LT recipients with obstructive CAD have post-transplant survival similar to LT recipients without angiographic evidence of obstructive CAD.

Methods

After Investigational Review Board approval, seven institutions (University of California Los Angeles, University of California San Francisco, University of Pittsburgh Medical Center,

Vanderbilt University, Mayo Clinic, Columbia University and Cleveland Clinic) reviewed the medical records of adult patients who underwent a primary LT over a 12 year period ending in December 2010 to identify patients whose pre-transplant evaluation included coronary angiography. Patients were identified by a search of the databases at each institution and followed through June 2011 to determine post-LT survival. The decision to perform pre-LT angiography was at the discretion of the treating physicians, and was not standardized between centers. Catheterization results were categorized as CAD positive (≥ 50% stenosis of one or more vessels), the CAD (+) group, or negative (< 50% stenosis), the CAD(-) group. Coronary stenoses of any major epicardial coronary artery were recorded; some centers reported stenoses of branches of the major coronary arteries. Positive angiography results were further stratified based on the degree of stenosis as severe CAD (>70% stenosis), the CADsev group, or moderate CAD (50-70% stenosis), the CADmod group. In the case of multiple coronary angiograms, the study prior to the LT was used in the analysis, except in those patients that underwent coronary interventions in which case the angiography performed prior to the intervention was used. Patients with a history of previous remote coronary intervention were stratified to the CADsev group.

Demographic characteristics and survival variables selected from the Scientific Registry of Transplant Recipients (SRTR) risk-adjustment models were compared between the CADsev, CADmod, and CAD(-) groups.[15] Demographic characteristics included age, gender, and model for end stage liver disease (MELD) score at the time of LT. Recipient risk factors for survival included a history of renal failure (identified by a history of pre-LT dialysis), life support (pre-LT mechanical ventilation), and post-LT re-transplantation (redo LT). Patients with a history of previous LT prior to angiography were excluded. Patients that underwent simultaneous liver kidney transplantation (SLKT) and living related liver transplantation (LRLT) were included.

Donor factors included in the analysis were donor age, race, height, cause of death, partial/split donor organ, donation after cardiac death (DCD), donor location (regional or national), and cold ischemia time (CIT).

All patients underwent standard perioperative surgical and anesthetic management as per the respective institutions. Date of angiography, date of coronary intervention(s) when applicable, date of LT, and date of death or last date of follow-up were recorded in all patients.

All cause post-LT mortality was recorded up to the last date of follow-up and was considered the primary outcome. The method of CAD treatment was categorized by type for each patient in the CAD(+) group. Invasive CAD treatment consisted of percutaneous transluminal coronary angioplasty (PTCA), bare metal coronary stenting (BMS), drug eluting coronary stenting (DES), coronary artery bypass graft surgery (CABG), and/or a combination of techniques.

Statistical Analyses

We compared demographic characteristics and risk factors across the CAD(-), CADmod, and CADsev groups. P values for comparing the groups were computed using the Kruskal-Wallis test for continuous variables or the chi square test for categorical variables. Survival curves by CAD groups were computed using the Kaplan-Meier method and compared across groups using the log rank test. We used Cox regression to assess the impact of CAD group on mortality before and after adjustment for the previously described recipient and donor covariates, using the no CAD group as the reference category. We reported the unadjusted and adjusted hazard ratios with corresponding confidence intervals and p-values using the Cox model. We computed the adjusted survival estimates in each group at six, 12, 24, and 36 months post-LT under the Cox model and compared the estimates in each CAD group with the CAD(-) group. Non-

inferiority was defined as a ≤ 10% reduction in survival in any of the CAD groups compared to the CAD(-) reference group. Therefore, if the lower confidence bound for the difference between any of the CAD groups and the CAD(-) group is less than 10%, we deem this difference non-inferior.

We performed additional analyses to examine the effect of pre-transplant coronary intervention on mortality using Cox regression. We used the Cox model-derived mortality rate ratios to assess for the effect of transplant center on mortality.

Based on preliminary data from a single center of 115 LT patients that underwent angiography prior to LT, we performed a power analysis to determine the sample size required to detect a 10% one-year mortality difference between CADsev and CAD(-) patients. This preliminary data demonstrated a 15% prevalence of CADsev (>70% stenosis) and a one year survival in the CAD(-) group of approximately 80%. For a desired power of 80% at a 0.05 significance level, with a median follow up of 30 months, a total sample size of approximately 640 patients is required (540 subjects in the CAD(-) group and 90 CADsev group).

Results

We identified a total of 630 LT patients that underwent pre-transplant angiography at the seven participating centers. Of the 630 patients that underwent preoperative angiography followed by LT, we identified 151 CAD(+) patients and 479 CAD(-) patients. The CAD(+) patients were further stratified by CAD severity into the CADsev (n=96) and CADmod (n=55) groups.

Demographic characteristics and recipient and donor organ covariates were compared between the CAD(-), CADmod, and CADsev groups (Table 2-1). The three groups differed significantly

by MELD ($p<0.0001$) and gender ($p<0.05$), and approached significance for recipient age ($p=0.06$) and donor cause of death ($p=0.06$). The mean MELD ranged from 21 to 26 and was highest in the CAD(-) group and lowest in the CADsev group. For all groups, the mean MELD was (22±8). There were more male patients in the CADmod (85%) and CADsev (78%) groups compared to the CAD(-) group (67%). Mean recipient age ranged from 58 to 61 and was slightly higher in the CADmod group. None of the other factors differed significantly between the groups. Overall, there were 55 simultaneous liver kidney transplants (SLKT) and 29 living donor liver transplants (LDLT). The prevalence of obstructive CAD in our patient population was 23.8%. The median follow-up (or time to death) in all patients was 24.5 months [8·9-45·0]. By patient group, the median follow-up was 22·4 [7·8-41·5] in the CAD(-) group, 25·8 [11·8-51·3] in the CADmod group, and 28·2 [14·1-55·2] in the CADsev group.

There were 161 deaths (26%) in the entire cohort. There were 44 deaths (29%) in the CAD(+) group and 117 deaths (24%) in the CAD(-) group. We compared survival between the patient groups before and after adjustment for the previously described recipient and donor risk factors (Table 2-2). There was no difference in both unadjusted and adjusted survival between the CAD(+) and CAD(-) groups (unadjusted HR=1.05; 95% CI=0.74-1.49, p=0.78, adjusted HR= 1.13; 95% CI: 0.79-1.62, p=0.493) (Figure 2-1A, 2-1B). We also compared survival in the CADmod and CADsev groups to the CAD(-) group before and after adjustment (Figure 2-1C, 2-1D). There was no difference in unadjusted and adjusted survival for both the CADsev group (unadjusted HR=1.17; 95% CI=0.78-1.74, p=0.44, adjusted HR=1.26; 95% CI 0.83-1.91, p=0.28) and the CADmod group (unadjusted HR=0.85; 95% CI=0.48-1.51, p=0.58, adjusted HR=0.93; 95% CI: 0.52-1.66, p=0.80). Higher MELD, redo LT, and national graft location were associated with higher mortality, while increased donor height was associated with a lower mortality (Table 2-3). In addition we compared adjusted survival in all CAD groups to the CAD(-)

group at the following times post-LT: six months, 12 months, 24 months, and 36 months (Table 2-4). The survival of the CAD(+) group was not inferior to the CAD(-) group in the first 24 months post-LT. The survival of the CADmod group was not inferior to the CAD(-) group in the first 36 months post-LT, and the survival of the CADsev group was not inferior to the CAD(-) group in the first six months post-LT.

There were 80 patients that underwent coronary interventions prior to LT (nine patients with moderate CAD and 71 patients with severe CAD): two patients underwent PTCA alone, 46 patients underwent stent placement (15 DES and 32 BMS), 32 patients underwent CABG (five underwent combined LT/CABG), and five patients underwent a combination of coronary interventions. There were 71 patients (47%) (25 in the CADsev group and 46 in the CADmod group) that received no pre-LT coronary intervention. Patients with a history of a remote coronary intervention prior to angiography were categorized as having severe CAD (n=17). To further examine the effect of pre-LT intervention on mortality, we divided all of the CAD patients (n=151) by the presence of intervention (n=80, 53%) and no intervention (n=71, 47%) and compared the unadjusted and adjusted survival of these two groups with the CAD(-) group (n=479) (Table 2-2). The intervention group had higher mortality compared to the CAD(-) group, which approached statistical significance (unadjusted HR=1.42; 95% CI:0.95-2.12, p=0.087, adjusted HR=1.45; 95% CI: 0.95-2.21, p=0.086) (Table 2-2).

We also investigated the center effect. There were significant differences between centers in number of patients, distribution of CAD groups, and MELD (p=0.0001). The effect of CAD group on mortality was unchanged after adjustment for center effect. We were unable to measure interactions between patient groups and centers as the sample sizes of each center were insufficient.

Discussion

The primary finding of this multi-center study is that, when current preoperative CAD treatment strategies are employed, survival after liver transplantation is similar in patients with and without obstructive CAD as documented by angiography. This is true before and after adjustment for donor and recipient risk factors. Furthermore, similar survival was observed between patients without angiographic evidence of CAD compared to patients with varying degrees of CAD severity.

We chose a survival difference of ten percentage points as significant since other known but not exclusionary risk factors for post-LT survival fall into this range, such as pre-LT mechanical ventilation, dialysis, and retransplantation.[16, 17] We chose to define obstructive CAD as 50% or greater diameter stenosis based on well-established standards.[18-21] We recognize that many patients in the CAD(-) group may actually have mild, non-obstructive CAD. We categorized the groups with no CAD and mild CAD together based on a report of similar long term mortality.[20] We chose patients without angiographic evidence of CAD as the comparator group to avoid the inclusion of patients who were evaluated exclusively with non-invasive CAD testing due to concerns over the lack of reliability of non-invasive CAD screening methods in the LT candidate population. [5, 10-14]

Previously, few patients over the age of 50 were referred for LT and advanced CAD was considered a contraindication to liver transplantation.[4] As the U.S. population ages, so does the cohort of patients with ESLD.[22] With improvements in post-LT outcomes, age limits for LT candidates have been relaxed, as illustrated by the increased number of patients over age 65 that have entered the UNOS waitlist.[22, 23] Early studies suggested that the prevalence of CAD in patients with ESLD was lower than the general population.[24] However, recent studies have

shown that the prevalence of CAD in LT candidates is equal to or greater than the general population, with a prevalence approaching 25%.[1-3]

Despite the prevalence of CAD in LT candidates, the impact of CAD on the survival of LT patients has not been extensively studied. In three studies that address the risk of CAD in LT candidates that underwent preoperative angiography, the number of patients with CAD is small, ranging from 21 to 47.[5-7] Furthermore, the mortality rates described in these studies vary considerably. In one of the earliest series reported by Plotkin, 32 LT recipients with angiographically-proven CAD had an overall mortality of 50% over a one to three year follow up period. Nearly a third of the deaths occurred within three months of LT.[4] Our data conflict with these results, suggesting that patients with a history of severe CAD, the majority of whom had undergone preoperative coronary intervention, can safely undergo LT and are not at a higher risk for short-term mortality. Our study was not designed to evaluate the effects of CAD treatment on post-LT survival. However, post-LT survival in patients with CAD appears to have improved over the last two decades, based upon our results compared to those of Plotkin. A combination of factors may be responsible, including improvements in the management of coronary risk factors, new drug therapy, and new interventional techniques. Of note, only one of the 32 patients in Plotkin's report was treated with a minimally invasive technique (PTCA), and none received stents. It is unclear to what degree a single factor, such as the availability of coronary stenting, accounts for the improvement in post-LT survival in patients with obstructive CAD.

We performed several additional exploratory analyses. We examined adjusted survival in the CAD(+), CAD sev, and CAD mod groups at fixed time points (Table 2-4). The difference in survival between the CAD(+) and CAD(-) groups appears similar (1.2-2.6% inferior in the

CAD(+) group) over 36 months. However, the certainty of this difference decreases over time (as exhibited by the widening confidence intervals) due to fewer patients in study. We also performed a subanalysis of the 80 CAD(+) patients that underwent a preoperative coronary intervention to compare their survival with the CAD(-) group, although our study was not a priori powered for this comparison (Table 2-2). This evaluation revealed a trend towards worse survival in patients that underwent preoperative coronary intervention. Long term (> one year) survival rates following interventions such as PCI and CABG are known to be inferior to patients without obstructive CAD. [20, 25, 26] OLT recipients with a significant burden of CAD, identified by the need for revascularization, may be expected to have a progression of their CAD following LT secondary to the effects of chronic immunosuppression.[27] Vigorous post-LT CAD surveillance and aggressive CAD risk factor modification in recipients with advanced CAD is warranted.

This study has a number of limitations. Our study was a retrospective analysis of previously recorded medical data from seven centers. Potential biases due to the retrospective nature of this study may have occurred; overall survival was chosen as our primary outcome to minimize bias. Nevertheless, bias may remain if we failed to adjust for covariates that affected survival. Furthermore, our patient groups are not representative of the overall pool of LT candidates. Patients that undergo angiography are older and have a higher likelihood of chronic illness. Overall survival in our patient cohorts is inferior to survival in an unselected population of adult LT recipients. Our methods of classifying patients to CAD(-) and CAD(+) groups were based solely on the angiography report in their medical records. There was no review of coronary angiograms by an independent reviewer; however, this reflects the current standard. There may have been center differences in the interpretation of coronary angiograms that went undetected in our analysis. Our definition of CAD as ≥ 50% stenosis is based on previously published studies of angiographic standards used to define clinically significant obstructive CAD.[18-21] The

degree of coronary stenosis that is clinically significant in the LT candidate is unknown, and does not take into account the presence of ruptured plaque or other pathology that is thrombogenic independent of obstructive CAD. The prevalence of CAD differed widely by center, reflecting differences in CAD detection and treatment paradigms that were not consistent. Exclusion criteria for transplant candidates may have differed by center, and patients that were denied transplantation or died prior to transplantation were not included in this analysis. Although we attempted to evaluate adjusted mortality by transplant center, the sample sizes at each center were too small to determine interactions between center and mortality. We did not include CAD risk factors as covariates in our analysis, since intermediary factors are highly correlated and not independent of angiographic results. Nevertheless, differences between the CAD(+) and CAD(-) groups in factors that affect survival through mechanisms other than CAD may have had an impact on survival that we could not detect.

This is the first multicenter study of survival in LT recipients with angiographically-proven CAD. When current CAD treatment strategies are employed there is no significant difference in post-LT survival between patients with and without obstructive CAD. The implications of these findings are significant. Given the aging of the LT candidate population, the known risks of cardiac disease, and the shortage of donor organs, our results demonstrate that patients with obstructive CAD can safely undergo LT and enjoy post-LT survival that is not inferior to patients without obstructive CAD.

Table 2-1. Descriptive statistics by CAD group			
	CAD (-) n=479	**CAD Moderate n=55**	**CAD Severe n=96**
MELD*	26.1 ± 10.0	23.9 ± 10.9	21.0 ± 8.9
Recipient Age (years)&	58.2 ± 7.6	60.7 ± 6.0	58.7 ± 6.6
Recipient Gender§			
Recipient Male	320 (66.8%)	47 (85.5%)	75 (78.1%)
Recipient Female	159 (33.2%)	8 (4.5%)	21 (21.9%)
Donor COD†			
Trauma	160 (34.2%)	12 (21.8%)	27 (29.0%)
Anoxia	82 (17.5%)	9 (16.4%)	19 (20.4%)
CVA	195 (41.7%)	26 (47.3%)	32 (34.4%)
Other	14 (3.0%)	4 (7.3%)	7 (7.5%)
Living Donor	17 (3.6%)	4 (7.3%)	8 (8.6%)

Data listed as mean ± SD or n (%). CAD = coronary artery disease; MELD = model end-stage liver disease; COD = cause of death; CVA=cerebrovascular accident.

* p<0.0001
& p=0.056
§ p=0.003
† p=0.058

Table 2-2. Summary of unadjusted and adjusted survival by CAD group				
	Unadjusted		Adjusted	
	HR (95% CI)	p-value	HR (95% CI)	p-value
CAD-negative	ref	--	ref	--
CAD-positive	1.05 (0.74, 1.49)	0.780	1.13 (0.79, 1.62)	0.493
CAD-negative	ref	--	ref	--
CAD-moderate	0.85 (0.48, 1.51)	0.576	0.93 (0.52, 1.66)	0.797
CAD-severe	1.17 (0.78, 1.74)	0.444	1.26 (0.83, 1.91)	0.277
CAD-negative	ref	--	ref	--
CAD-no intervention	0.67 (0.39, 1.17)	0.164	0.79 (0.45, 1.39)	0.409
CAD-intervention	1.42 (0.95, 2.12)	0.087	1.45 (0.95, 2.21)	0.086

CAD = coronary artery disease; HR = hazards ratio; CI = confidence interval; ref = reference group

Table 2-3. Cox regression results for the assessment of CAD group versus mortality after LT adjusting for the covariates

Recipient Factors	HR (95% CI)	p-value
MELD (per unit)	1.04 (1.02, 1.06)	<0.001
Recipient Age >55 years	1.30 (0.92, 1.84)	0.143
H/o dialysis	0.69 (0.43, 1.08)	0.106
Life support	1.29 (0.71, 2.35)	0.394
Redo LT	2.82 (1.67, 4.78)	<0.001
Donor Factors	**HR (95% CI)**	**p-value**
DCD Graft	1.45 (0.77, 2.74)	0.251
Donor Age (years)	1.01 (1.00, 1.02)	0.079
Donor Height (cm)	0.98 (0.97, 1.00)	0.006
Partial / Split Graft (vs whole)	♮	--
CIT (per hour)	♮	--
Location: Regional (vs Local)	1.14 (0.80, 1.61)	0.468
Location: National (vs Local)	1.66 (1.02, 2.69)	0.041
Donor COD: Trauma*	1.22 (0.84, 1.76)	0.295
Donor COD: Other*	1.44 (0.71, 2.91)	0.314
Donor Race: Afr Amer (vs White)	♮	--
Donor Race: Other (vs White)	♮	--

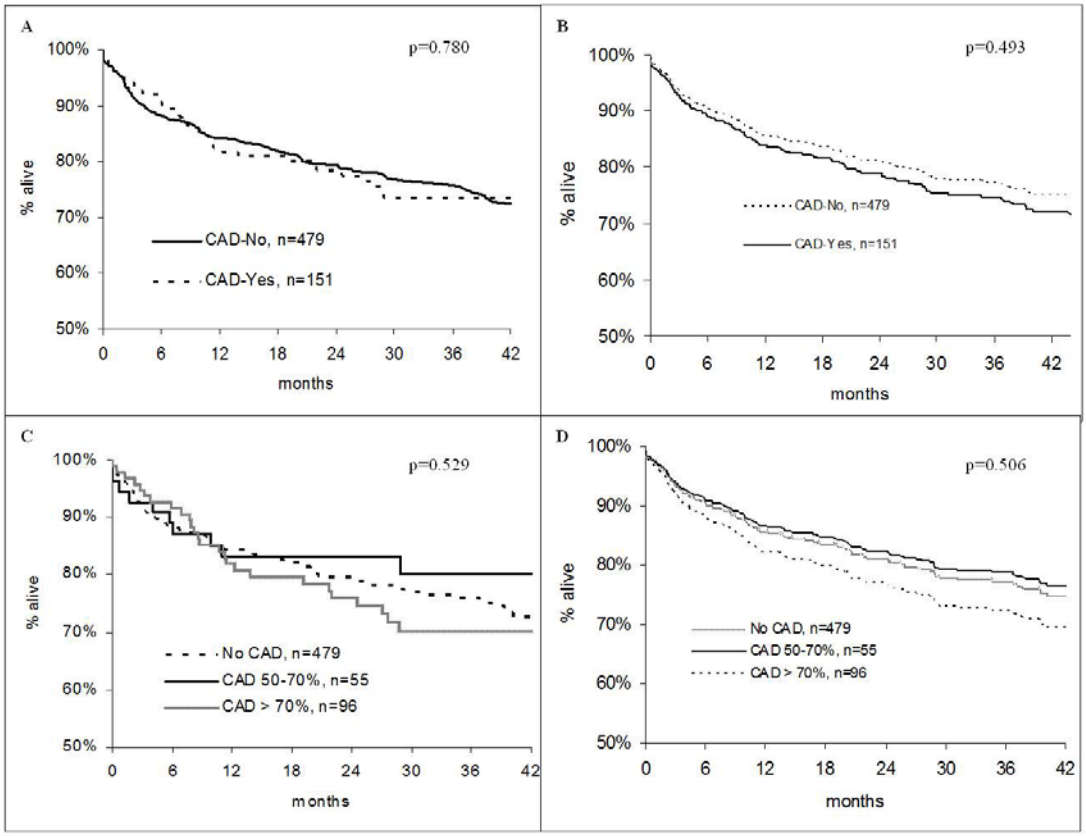
CAD = coronary artery disease; LT = orthotopic liver transplant; HR = hazards ratio; CI = confidence interval; Tx = transplant; MELD = model end-stage liver disease; DCD = donation after cardiac death; CIT = cold ischemia time; COD = cause of death. *vs anoxia/CVA/living donor. ♮ not included in final model because p>0.15 and 0.8<HR<1.2.

Table 2-4. Adjusted survival by group: CAD (-), CAD (+), CADmod and CADsev (non-inferiority assessments)

	Adjusted survival by group			Adjusted % difference in survival vs CAD (-) group	
Months FU	**CAD (-)**		**CAD (+)**	**CAD (+)**	
6	90.4 ± 1.2%		89.2 ± 1.9%	-1.2% (-5.65, 3.22%)	
12	85.7 ± 1.6%		83.9 ± 2.5%	-1.8% (-7.63, 4.12%)	
24	81.2 ± 1.9%		78.9 ± 3.1%	-2.2% (-9.37, 4.90%)	
36	77.3 ± 2.2%		74.7 ± 3.6%	-2.6% (-10.88, 5.63%)	
Months FU	**CAD (-)**	**CAD Moderate**	**CAD Severe**	**CAD Moderate**	**CAD Severe**
6	90.4 ± 1.2%	91.1 ± 2.5%	88.1 ± 2.4%	0.7% (-4.9, 6.2%)	-2.3% (-7.6, 2.9%)
12	85.7 ± 1.6%	86.7 ± 3.6%	82.3 ± 3.2%	1.0% (-6.7, 8.8%)	-3.4% (-10.4, 3.7%)
24	81.2 ± 1.9%	82.5 ± 4.6%	77.0 ± 4.0%	1.3% (-8.4, 11.0%)	-4.3% (-12.9, 4.4%)
36	77.3 ± 2.2%	78.8 ± 5.4%	72.3 ± 4.6%	1.5% (-9.9, 12.9%)	-5.0% (-14.9, 5.0%)

CAD = coronary artery disease; FU =follow-up; Adjusted survival data presented as % survival ± SE; Adjusted % difference in survival data presented as % difference (95% CI)

Figure 2-1. Unadjusted and adjusted survival curves for patient groups



(A) Unadjusted survival: CAD-positive and CAD-negative groups, (B) Adjusted survival: CAD-positive and CAD-negative groups, (C) Unadjusted survival: CAD-negative, moderate CAD, and severe CAD groups, (D) Adjusted survival: CAD-negative, moderate CAD, and severe CAD groups

References

1. Carey WD, Dumot JA, Pimentel RR, et al. The prevalence of coronary artery disease in liver transplant candidates over age 50. *Transplantation.* Mar 27 1995;59(6):859-864.

2. Keeffe BG, Valantine H, Keeffe EB. Detection and treatment of coronary artery disease in liver transplant candidates. *Liver Transpl.* Sep 2001;7(9):755-761.

3. Tiukinhoy-Laing SD, Rossi JS, Bayram M, et al. Cardiac hemodynamic and coronary angiographic characteristics of patients being evaluated for liver transplantation. *Am J Cardiol.* Jul 15 2006;98(2):178-181.

4. Plotkin JS, Scott VL, Pinna A, Dobsch BP, De Wolf AM, Kang Y. Morbidity and mortality in patients with coronary artery disease undergoing orthotopic liver transplantation. *Liver Transpl Surg.* Nov 1996;2(6):426-430.

5. Harinstein ME, Flaherty JD, Ansari AH, et al. Predictive value of dobutamine stress echocardiography for coronary artery disease detection in liver transplant candidates. *Am J Transplant.* Jul 2008;8(7):1523-1528.

6. Diedrich DA, Findlay JY, Harrison BA, Rosen CB. Influence of coronary artery disease on outcomes after liver transplantation. *Transplant Proc.* Dec 2008;40(10):3554-3557.

7. Yong CM, Sharma M, Ochoa V, et al. Multivessel Coronary Artery Disease Predicts Mortality, Length of Stay, and Pressor Requirements After Liver Transplantation. *Liver Transplant.* Nov 2010;16(11):1242-1248.

8. Ehtisham J, Altieri M, Salame E, Saloux E, Ollivier I, Hamon M. Coronary artery disease in orthotopic liver transplantation: pretransplant assessment and management. *Liver Transpl.* May 2010;16(5):550-557.

9. Raval Z, Harinstein ME, Skaro AI, et al. Cardiovascular risk assessment of the liver transplant candidate. *Journal of the American College of Cardiology.* Jul 12 2011;58(3):223-231.

10. Donovan CL, Marcovitz PA, Punch JD, et al. Two-dimensional and dobutamine stress echocardiography in the preoperative assessment of patients with end-stage liver disease prior to orthotopic liver transplantation. *Transplantation.* Apr 27 1996;61(8):1180-1188.

11. Plotkin JS, Benitez RM, Kuo PC, et al. Dobutamine stress echocardiography for preoperative cardiac risk stratification in patients undergoing orthotopic liver transplantation. *Liver Transpl Surg.* Jul 1998;4(4):253-257.

12. Tsutsui JM, Mukherjee S, Elhendy A, et al. Value of dobutamine stress myocardial contrast perfusion echocardiography in patients with advanced liver disease. *Liver Transplant.* Apr 2006;12(4):592-599.

13. Davidson CJ, Gheorghiade M, Flaherty JD, et al. Predictive value of stress myocardial perfusion imaging in liver transplant candidates. *Am J Cardiol.* Feb 1 2002;89(3):359-360.

14. Aydinalp A, Bal U, Atar I, et al. Value of stress myocardial perfusion scanning in diagnosis of severe coronary artery disease in liver transplantation candidates. *Transplant Proc.* Nov 2009;41(9):3757-3760.

15. Anonymous. Scientific Registry of Transplant Recipients. *Risk-Adjustment Models (Transplant Programs)* 2012; http://www.srtr.org/csr/current/modtabs.aspx. Accessed February 10, 2012.

16. Desai NM, Mange KC, Crawford MD, et al. Predicting outcome after liver transplantation: utility of the model for end-stage liver disease and a newly derived discrimination function. *Transplantation.* Jan 15 2004;77(1):99-106.

17. Olthoff KM, Brown RS, Delmonico FL, et al. Summary report of a national conference: Evolving concepts in liver allocation in the MELD and PELD era. *Liver Transplant.* Oct 2004;10(10):A6-A22.

18. Lozner EC, Johnson LW, Johnson S, et al. Coronary Arteriography 1984-1987 - A report of the Registry of the Society for Cardiac Angiography and Interventions 2. An analysis of 218 deaths related to coronary arteriography. *Catheterization and Cardiovascular Diagnosis.* May 1989;17(1):11-14.

19. Bashore TM, Bates ER, Berger PB, et al. American College of Cardiology/Society for Cardiac Angiography and Interventions Clinical Expert Consensus Document on cardiac catheterization laboratory standards. A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol.* Jun 15 2001;37(8):2170-2214.

20. Kemp HG, Kronmal RA, Vlietstra RE, Frye RL. 7 year survival of patients with normal or near normal coronary arteriograms - A CASS Registry study. *Journal of the American College of Cardiology.* Mar 1986;7(3):479-483.

21. Baptista J, Arnese M, Roelandt JR, et al. Quantitative coronary angiography in the estimation of the functional significance of coronary stenosis: correlations with dobutamine-atropine stress test. *J Am Coll Cardiol.* May 1994;23(6):1434-1439.

22. Lipshutz GS, Busuttil RW. Liver transplantation in those of advancing age: the case for transplantation. *Liver Transpl.* Oct 2007;13(10):1355-1357.

23. Keswani RN, Ahmed A, Keeffe EB. Older age and liver transplantation: A review. *Liver Transplant.* Aug 2004;10(8):957-967.

24. Turner TB, Bennett VL, Hernandez H. The beneficial side of moderate alcohol use. *The Johns Hopkins medical journal.* Feb 1981;148(2):53-63.

25. Stettler C, Wandel S, Allemann S, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *Lancet.* Sep 15 2007;370(9591):937-948.

26. Serruys PW, Ong ATL, van Herwerden LA, et al. Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease - The final

analysis of the arterial revascularization therapies study (ARTS) randomized trial. *Journal of the American College of Cardiology.* Aug 16 2005;46(4):575-581.

27. Rabkin JM, Corless CL, Rosen HR, Olyaei AJ. Immunosuppression impact on long-term cardiovascular complications after liver transplantation. *Am J Surg.* May 2002;183(5):595-599.

Chapter 3 - Statistical Analysis

Overview

The impact of coronary artery disease (CAD) on overall survival after liver transplantation (LT) was examined in 630 adult liver transplant patients who underwent LT at seven centers. Out of the total patients, 479 had no CAD (no stenosis >= 50% in any coronary artery), 55 had moderate CAD (stenosis of 50-70% of one or more coronary arteries) and 96 had severe CAD (stenosis > 70% of one or more coronary arteries). We examined the impact of CAD group on mortality before and after adjustment for up to 8 recipient and up to 8 donor covariates.

The following 8 recipient covariates were considered in the analysis: MELD score, age at OLT, gender, combined liver kidney transplant (y/n), history of dialysis (y/n), need for life support (intubated prior to OR) (y/n), prior transplant (y/n) and pre OLT CAD intervention (y/n). The following 8 donor covariates were considered in the analysis: age, cause of death (trauma, anoxia, CVA, other, living donor), donation after cardiac death (DCD) (y/n), partial or split allograft (y/n), height, location (local, regional, national) and cold ischemia time (CIT).

Statistical Methods

Descriptive

We compared risk factors across the CAD groups to assess whether groups were comparable. P-values for comparing the groups were computed using the Wilcoxon rank sum test (continuous variables) or the chi square test (categorical variables).

Assessment of patient survival

Survival curves by CAD group were computed using the Kaplan-Meier method and compared across groups using the log rank test. We used Cox regression to assess the impact of CAD group on mortality before and after adjustment for up to 16 recipient and donor covariates, using

the “no CAD” group as the reference category. Since we determined that the impact of CAD group on mortality tended to differ based on CAD severity after controlling for the covariates, we decided not to combine the CAD groups but examined the groups separately. The adjusted model allowed for interactions between CAD group versus 6 recipient factors including MELD, age, combined liver kidney transplant, history of dialysis, need for life support and prior transplant and versus 3 donor factors including age, DCD and CIT. Interaction effects were tested using $p<0.1$. Main effects were selected in the final model using the backwards stepwise procedure with liberal $p<0.15$ as the retention criteria. In addition, any variable known to be clinically important and with HR > 1.2 was also retained. We adopted slightly more liberal criteria for selection of main effects as this is an exploratory study and we did not wish to miss a potentially important covariate as this could have potentially biased the results. Reported are the unadjusted and adjusted hazard ratios with corresponding confidence intervals and p-values under the Cox model.

Missing values

Donor variables for COD, race, graft type, location, age, height and CIT had some values missing, with proportion of missing values ranging from 2.2% to 9.7%. All missing values were singly imputed prior to the multivariate analysis using regression imputation. We impute the missing values since imputation is generally less biased than retaining only the complete cases in the analysis, as the latter method excludes a large amount of data including non missing data and this is known to introduce even more bias in the analysis than the imputation procedure itself.

As an aside, we examined the cross tabulations of center versus group and center versus MELD score.

Results

Table 2-1 shows the descriptive summary statistics by group. The groups significantly or marginally differed by MELD, recipient age, recipient gender, donor COD. None of the other factors significantly differed across groups, and are not illustrated in the Table (but described in the text).

Table 2-2 compares the unadjusted and adjusted patient survival across the two (neg/pos) and three (neg, mod, severe) CAD groups. The hazard ratios, with 95% confidence intervals and p-values, using "neg CAD" as the reference group, are included. The bottom panel compares the unadjusted and adjusted survival by CAD intervention (revascularization) using the following groups: CAD neg, CAD positive with no pre-LT intervention, and CAD positive with pre-LT intervention.

Table 2-3 shows the Cox regression results for the assessment of CAD group on mortality after adjustment for the covariates. We did not find significant interactions between CAD group versus any of the donor and recipient factors, with exception of donor age. The above hazard ratios summarize the average effect of CAD group on mortality across all donor ages. However, in a subsequent analysis that also allowed for group by donor age interaction, we find that the association between severe CAD and greater mortality as reported above disappears at younger donor ages and remains significant only at older donor ages.

Table 2-4 examines adjusted survival at discrete follow-up times by CAD group. The top panel stratifies by two CAD groups (CAD neg/CAD pos), while the bottom panel stratifies survival by three groups (CAD neg/CAD mod/CAD severe). The right-most column illustrates the difference

in survival between the various groups and the reference group (CAD neg), with 95% CI provided.

Figure 2-1 contains 4 panels that plot the patient survival curves according to two groups (CAD neg/CAD pos) in panels A and B (unadjusted and adjusted, respectively) and according to three groups (CAD neg/CAD mod/CAD severe) in panels C and D (unadjusted and adjusted, respectively).

Limitations

The retrospective nature of the study introduces a selection bias. Patients who were selected for coronary angiography were not selected randomly from the pool of liver transplant candidates but rather at the discretion of the treating physicians at the seven participating sites. These patients undoubtedly represented an older, more sedentary cohort of candidates with a higher proportion of coronary disease risk factors such as diabetes, hypertension, and hyperlipidemia. The increased likelihood of non-ambulatory status represented a non-reassuring finding that further served to select patients with high acuity. In many cases their inactivity may have resulted from being confined to the intensive care unit or being ventilator dependent. However, since this knowledge was used to determine who underwent angiography any bias affects both groups, those found by angiography to have obstructive coronary disease and those without positive angiographic findings. However, survival for both groups cannot be compared to post-transplant survival for unselected patients.

An additional selection bias was introduced by the lack of standardization of the criteria used in each of the participating sites to select patients for angiography. Among the various centers cardiologists may have been more or less likely than their colleagues to recommend

angiography. While this introduces bias, it also represents real world care, and in the absence of evidence indicating best practice, a retrospective study is the first step in clarifying whether coronary artery disease contraindicates liver transplantation.

Yet another selection bias was introduced through the use of multiple inclusion criteria: patients were required to undergo coronary angiography followed by liver transplantation. Patients with inoperable coronary disease, who were identified during angiography but denied access to liver transplantation, were excluded from the study group. This represents another exclusion that further narrowed the pool of patients available for inclusion in the study. We were unable to quantify the number of patients excluded after angiography since we identified patients using the transplant registry. A prospective study could shed light on the number of patients excluded as a result of angiographic findings.

Measurement biases may have occurred during the interpretation of angiography, which was performed in standard fashion using real-time visualization in the catheterization laboratory without the aid of computerized measurements. While computerized measurements are available, they are typically used only during research and not during routine clinical care. Again, this represents a real world approach. However, this bias would most likely be random rather than systematic. Nonetheless, a prospective study would permit the use of computerized measurements of angiographic findings.

Intervention bias undoubtedly occurred since the criteria used to determine whether intervention was used for coronary stenosis was not standardized. Some patients with moderate stenosis (9 of 55) underwent interventions, while some patients with severe stenosis did not (25 of 96). Because of the retrospective nature of the study this finding cannot be explained.

Lastly, the outcome of interest in our proportional hazards model was all-cause mortality. Cardiovascular related deaths would seem to be a better outcome; however, the cause of death was unable to be ascertained in many patients. This limitation would also apply in a prospective study. For instance, patients who died of cardiac arrest while being treated for sepsis, or those patients found dead at home are impossible to classify accurately. As a result we are unaware of whether any differences in survival are related to coronary artery disease, or due to differences in other known causes of post-transplant mortality such as organ rejection, infection or malignancy. Our model assumes that non-cardiac causes of death would be similarly distributed among patients with and without obstructive coronary artery disease, and that any differences in survival are due to coronary disease.

In addition to clinical biases, biases related to the statistical methodology could have occurred. The Cox proportional hazards method assumes that the survival rate does not change disproportionally over time. It is known that mortality is greatest in the immediate post-operative period, and that mortality after liver transplantation has improved over the last several decades. These changes would affect both the CAD positive and negative groups so these assumptions may not be violated. Additionally the Cox model assumes that survival of the censored subjects is similar to the survival of the remaining subjects. Whether this is true is often unknown.

An additional statistical problem is adjustment for covariates. Given the sample size of the study, a limited number of covariates were chosen for inclusion in the model. Since every known covariate was not included in the model, the model may not predict survival as accurately as it could. Had the model been based upon a larger sample size and a wider range of covariates,

accuracy would improve. Nonetheless, this is the largest study of coronary artery disease in liver transplant recipients to date.

Alternative Analysis Strategies

A number of alternative analysis strategies can be used to evaluate survival data. These include propensity score matching, binary recursive partitioning (also known as CART) and artificial neural networks (ANN). Each of these methods has potential advantages.

Propensity matching

The idea behind propensity matching is to select a group of non-beneficiaries such that they resemble the beneficiaries in everything except the attribute (or intervention) under consideration. This simulates random assignment to the control group; however, the comparability of the control group to the intervention group accounts only for observable characteristics, not unobserved characteristics, as is the case with randomization.

When the number of characteristics to match is large, matching is difficult to achieve on each characteristic. This problem is overcome by matching the groups using a “propensity score” that summarizes the observable characteristics of the groups.[1]

Using a single propensity score simplifies matching from a multi-dimensional problem to a one-dimensional one. Once the match is complete and the two groups are formed, the average effect can be assessed by computing the difference in means between the two groups. All variables that affect the outcome of interest should be included in the match, though this is practically difficult to achieve. For example, in the current study the likelihood of having coronary

artery disease (or of having an intervention for CAD) is influenced by coronary risk factors, which were not collected (or included) in the proportional hazards model.

The advantage of matching over standard regression methods such as proportional hazards results from a reduction in the number of covariates to a single score. This allows the model to account for more covariates than standard regression methods. It also does not impose linear relationships on the covariates in the way that standard regression does.

Binary Recursive Partitioning (also known as Classification and Regression Trees, or CART) and Artificial Neural Networks (ANN)

CART splits parent nodes into two child nodes (decisions are binary). Child nodes are treated as parent nodes and can be split again into two nodes. This recursive process creates trees governed by rules that define terminal nodes, or outcomes.

Artificial neural networks (ANN) are another computer-generated technique that recognizes patterns by adjusting weights in response to data input. With increased data input, training occurs. In a study in which lipid levels were used to predict the likelihood of CAD, neural networks outperformed Cox regression.[2] ANN are beneficial in modeling nonlinear relationships. However, ANNs do not provide the same level of understanding of relationships between predictors as that provided by the relative risk generated by Cox proportional hazards models.

Theoretical advantages of CART include efficiency in discovering interactions and producing results in terms that clinically clear.[3] However, when CART was used with several datasets to predict disease recurrence in cancer patients, Cox methodology performed comparably or superior to CART and neural networks. [4]

In conclusion, Cox proportional hazards regression is the standard statistical methodology for the comparison of survival between groups. Newer, computer-generated techniques are often compared to proportional hazards methodology. In some instances newer techniques such as recursive partitioning and neural networks may be comparable or even superior. However, these techniques are best used to supplement traditional analyses.

References

1. Austin PC. A critical appraisal of propensity-score matching in the medical literature between 1996 and 2003. *Statistics in medicine.* May 30 2008;27(12):2037-2049.

2. Lapuerta P, Azen SP, LaBree L. Use of neural networks in predicting the risk of coronary artery disease. *Computers and biomedical research, an international journal.* Feb 1995;28(1):38-52.

3. Ciampi A, Thiffault J, Nakache J, Asselain B. Stratification by stepwise regression, correspondence analysis and recursive partition: A comparison of three methods of analysis for survival data with covariates. *Computational Statistics & Data Analysis.* 1986;4:185-204.

4. Kattan MW. Comparison of Cox regression with other methods for determining prediction models and nomograms. *The Journal of urology.* Dec 2003;170(6 Pt 2):S6-9; discussion S10.