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Pre-Liver Transplant Cardiac Catheterization is Associated with Low Rate of Myocardial Infarction and Cardiac Mortality

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Abbreviations:

CAD: coronary artery disease

CATH: cardiac catheterization

CCTA: coronary computed tomography angiography

EKG: electrocardiogram

LT: liver transplant

MI: myocardial infarction

PCI: percutaneous coronary intervention

SE: stress echocardiogram

WMA: wall motion abnormalities

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Abstract

Background: A previous study at Indiana University demonstrated a reduction in myocardial infarction (MI) incidence with increased frequency of cardiac catheterization (CATH) in liver transplant (LT) candidates. A strict protocol for performing CATH based upon predefined risk factors, rather than non-invasive testing alone, was applied to a subgroup (2009-2010) from that study. CATH was followed by percutaneous coronary intervention (PCI) in cases of significant coronary artery disease (CAD; ≥50% stenosis). The current study applies this screening protocol to a larger cohort (2010-2016) to assess post-LT clinical outcomes.

Results: Among 811 LT patients, 766 underwent stress testing (94%), and 559 underwent CATH (69%) of whom 10% had CAD requiring PCI. The sensitivity of stress echocardiography in detecting significant CAD was 37%. Predictors of PCI included increasing age, male gender and personal history of CAD ($p<0.05$ for all). Compared to patients who had no CATH, patients who underwent CATH had higher mortality ($p=0.07$), and the hazard rates (HR) for mortality increased with CAD severity [normal CATH (HR: 1.35 [95% CI: 0.79, 2.33], $p=0.298$); non-obstructive CAD (HR: 1.53 [95% CI: 0.84, 2.77], $p=0.161$); and significant CAD (HR: 1.96 [95% CI: 0.93, 4.15], $p=0.080$)]. Post-LT outcomes were compared to the 2009-2010 subgroup from the previous study and showed similar 1-year overall mortality (8% and 6%, $p=0.48$); 1-year MI incidence (<1% and <1%, $p=0.8$); and MI deaths as portion of all deaths (3% and 9%, $p=0.35$).

***Conclusion*:** Stress echocardiography alone is not reliable in screening LT patients for CAD. Aggressive CAD screening with CATH is associated with low rate of MI and cardiac mortality and validates the previously published protocol when extrapolated over a larger sample and longer follow-up period.

Background

The prevalence of coronary artery disease (CAD) is rising among LT candidates. Approximately 25% of LT candidates with traditional coronary risk factors may have moderate CAD (stenosis ≥ 50%) even while asymptomatic, and those with severe CAD have increased cardiac mortality (1). Therefore, aggressive pre-LT ischemic evaluation is necessary to assess cardiac function and identify clinically significant cardiovascular disease. Current pre-LT guidelines endorse initial assessment with electrocardiogram (EKG) and non-invasive stress testing (2, 3). The 2012 American Heart Association/American College of Cardiology Foundation Scientific Statement for Cardiac Disease Evaluation and Management among Kidney and Liver Transplant Candidates recommend screening with non-invasive modalities in patients with 3 or more cardiac risk factors, regardless of functional status (3). The American Association for the Study of Liver Diseases Practice Guideline was updated in 2013 to recommend stress echocardiogram (SE), whether exercise or pharmacologic, as the initial cardiovascular screening tool in all LT candidates (2).

Despite these recommendations, there is a large degree of variation between clinical practice guidelines and transplant center practice patterns with regards to who should be screened for CAD and which screening modality should be used (4, 5). Moreover, the clinical utility of screening asymptomatic transplant candidates remains unclear. Large randomized controlled trials for non-transplant patients do not recommend screening and revascularization of asymptomatic patients preoperatively, although these trials might not be applicable to the transplant population, where asymptomatic disease is prevalent (3). Moreover, LT candidates are at risk of hemodynamic instability due to organ dysfunction that extends beyond the cardiac system (6). Risk stratification of LT candidates remains challenging as data on cardiovascular mortality post-transplantation are based on incremental knowledge from observational studies; there are no randomized controlled trials that compare different screening modalities. Moreover, Framingham's score and traditional scores do not accurately predict cardiovascular risk score in the preoperative transplant patients (7). In context of the aforementioned, further analysis of specific risk factor combinations with respect to outcomes would allow for more selective use of cardiac evaluation, especially given that risk stratification may be a better predictive tool than stress testing in the transplant population (8).

An analysis of 1221 LT patients at Indiana University Hospital found significant reduction in 1-year all-cause mortality, and in the incidence of MI post-transplant, with increased frequency of CATH and percutaneous coronary intervention (PCI) over 3 time periods between 2000-2010 (9). Period A (2000-2004) included 527 patients who were initially referred to general cardiology, all of them had a 2-dimensional echocardiogram, and CATH was at the discretion of the consulting cardiologist. Period B (2005-2008) included 520 patients who were evaluated by select cardiologists, and these patients underwent SE with or without CATH. Period C (2009-2010) included 174 patients who were evaluated by a single cardiologist. Since 2009, our center has adopted a policy of cardiac evaluation by a single cardiologist including stress testing and CATH. CATH was indicated based on risk factors even in the presence of negative stress test findings. These risk factors included age, smoking history, diabetes, hypertension requiring medications, history of CAD, family history of CAD, and obesity. A lower threshold for PCI was adopted at ≥50% stenosis in a major vessel (left anterior descending artery or right coronary artery) or critical disease, defined as stenosis ≥70% in at least moderate-sized branch vessels.

This study is a follow-up of the previous analysis and will help in further understanding cardiovascular disease in the LT population. The objective of this study is twofold. First, it builds on the previous study by further analyzing the role of universal stress testing and use of CATH based on predefined risk factors over a longer duration (2010-2016) and in a larger population. The efficacy of stress testing alone to identify CAD in the liver failure population will be assessed. Second, this study reports the long-term outcomes of an aggressive CAD screening protocol with CATH based on risk factors, and a lower threshold for coronary intervention. One-year all-cause mortality, 1-year MI incidence, and MI deaths are reported, as well as long-term survival.

Methods

Data Collection

All patients undergoing LT at a single center between 2010 and 2016 were evaluated by a single cardiologist. The record of each of these patients was reviewed individually and collected data included: demographics (date of transplant, age at transplant, gender), etiology of cirrhosis, number of grafts (if more than one),

ejection fraction, CATH status (if patient underwent CATH; degree of stenosis, whether there was an intervention or not, and immediate complications), initial stress testing status and the associated result in case of SE (normal test, abnormal echocardiogram component, abnormal EKG component but normal echocardiogram component, non-diagnostic test) or nuclear test (normal or abnormal). Data related to the following cardiovascular risk factors were also analyzed: body mass index, diabetes mellitus, hypertension requiring medications, tobacco use (never user, current user at the time of evaluation, former user, and number of tobacco pack-years if there was a smoking history), personal history of CAD, and family history of CAD (negative, immediate, or distant family history). Collection of pre- and post-CATH laboratory values can be found in **Supplement 1**. Data were stored and updated on an online secure password-protected access-controlled portal. Only personnel with approval from our Institutional Review Board and who had Indiana University credentials were given access to the database.

Definitions: CATH Results

CATH results were defined as negative (no intervention) or positive (CAD ≥50% stenosis in a major vessel or ≥70% stenosis in at least a moderate-sized branch vessel requiring intervention with PCI +/- balloon angioplasty). Degree of stenosis was classified into three categories: normal coronaries, non-obstructive CAD (<50% stenosis; or ≥50% stenosis but not in a major vessel and not requiring intervention; or revascularized CAD; or luminal irregularities; or minor calcifications), or significant CAD (≥50% stenosis in a major vessel or ≥70% stenosis in at least a moderate-sized branch vessel warranting intervention).

Definitions: SE Results

SE results were defined as negative, positive, or non-diagnostic. A test was deemed negative if there were no wall motion abnormalities (WMA) with stress, no EKG changes, and no chest pain; or the SE component was normal with baseline EKG abnormalities or equivocal EKG component. A positive stress test had WMA (new or worsening with stress) +/- EKG changes +/- chest pain; or positive EKG changes per criteria without WMA (10). A stress test was considered non-diagnostic if it had equivocal findings; or 85% of maximum predicted heart rate (220-age) was not achieved; or the test was terminated due to fatigue, hypotension, hypertension, arrhythmia, or dyspnea without chest pain.

Our CATH Protocol

Femoral approach was used in all cases along with a combined fluoroscopic and Doppler ultrasound technique for access. Further details can be found in **Supplement 2**. Drug-eluting stents were routinely used since 2009 with at least 3 months of dual antiplatelet therapy, except for two patients who received at least 6-8 weeks of therapy due to the need for urgent LT. Dual antiplatelet therapy was generally restarted post-LT to continue for a total of 1 year post-PCI.

Postoperative MI and Cardiac Mortality

LT outcomes and deaths were followed and recorded by the Department of Surgery staff members. To identify 1-year cardiac mortality, the record of each patient who received LT during 2010-2016 and died was reviewed individually. The incidence of postoperative MI within 1 year after transplant date was investigated using International Classification of Diseases Ninth Revision Clinical Modification (ICD-9-CM) diagnosis codes, ICD-10-CM diagnosis codes, as well as troponin values. Troponin value of 0.03 ng/ml was used as the upper limit of normal which meets the 99th percentile for normal range troponin values. Obtained values were filtered according to two times the upper limit of normal (>0.06 ng/ml). A total of 125 patients met the criteria, and their charts were reviewed individually. MI was defined as a troponin value more than two times the upper limit of normal with supporting evidence of EKG changes and clinical presentation.

Statistical Analysis

We used frequency distribution to describe the proportion of patients undergoing cardiac stress testing and CATH in terms of factors such as patient demographics, cardiac risk factors, Model for End-stage Liver Disease score, and graft number. Bivariate analysis using Chi-square and Fisher's exact tests, as appropriate, were conducted to examine the relationship between the aforementioned factors and results from cardiac stress testing or CATH. Unadjusted Kaplan-Meier analysis and age-adjusted Cox proportional hazards models were used to perform the survival analysis post-LT. The log-rank test was used to compare differences in survival across CATH groups. All hypotheses were tested at 0.05 level of significance and the data analysis was done in

Stata version 14 (StataCorp, College Station, TX, USA). Use of center data for retrospective analysis has been reviewed and approved by the Indiana University Institutional Review Board. The study protocol for this research conformed to the Declaration of Helsinki.

Results

Demographics

Data for a total of 811 LT patients were included in this analysis. The cohort's median Model for End-stage Liver Disease score was 22, age 57 years, body mass index 28 kg/m^2, with 67% males, and 89% identified as Caucasians **(Table 1)**. Regarding common cardiac risk factors, 30% were diabetic, 39% with hypertension, 50% with any history of tobacco use, 7% had a personal history of CAD and 37% with immediate family history of CAD. The most common etiologies for cirrhosis were hepatitis C (30%), followed by alcoholic liver disease (22%), and non-alcoholic steatohepatitis (20%). Of note, many patients had more than one factor contributing to their liver disease. Other less common cirrhosis etiologies are listed in **Supplemental Table 1**.

Stress Testing Results

There were 811 patients who underwent LT during the study period, of whom 766 had stress testing (94%) **(Figure 1, Table 2).** Notably, this refers to an initial stress test prior to CATH, if CATH was done. For example, 8 patients already had prior CATH at the time of evaluation when a subsequent stress test was obtained; these were counted among patients who did not undergo initial stress testing. SE was normal in 613 (80%) patients. SE was abnormal in 63 (8%) patients, of whom 37 (59%) patients had WMA and 26 (41%) patients had EKG changes but normal SE component. Non-diagnostic SE were reported in 66 (9%) patients. Significant differences ($p \leq 0.05$) between SE result categories were found in diabetes mellitus and personal history of CAD **(Table 2)**. Nuclear stress testing was performed in 24 (3%) patients, 21 (88%) of which were normal and 3 (13%) of which were abnormal.

CATH Results

Total number of patients who had CATH was 559 (69%) patients **(Table 3)**. Coronary arteries were found to be normal in 314 (56%) patients, non-obstructive CAD was found in 190 (34%) patients, and significant or obstructive CAD requiring intervention was found in 55 (10%) patients. Among the 55 patients who underwent CATH with PCI, 29 (53%) had PCI to the left anterior descending artery, 14 (25%) to the right coronary artery, 8 (15%) to the left circumflex artery, 3 (5%) to the posterior descending artery, 7 (13%) to a diagonal branch, and 6 (11%) to a marginal branch. Sixteen patients (29%) had PCI to two or more coronary arteries and/or branches. Significant differences ($p \leq 0.05$) between the normal coronaries, non-obstructive CAD, and significant CAD groups were found in age, gender, hypertension, diabetes mellitus, and personal history of CAD **(Table 3)**. Characteristics of patients who had positive CATH and negative CATH were compared **(Figure 2)**.

Immediate CATH-related complications were seen in 6 (1%) patients; 3 with positive CATH, and 3 with negative CATH **(Table 3)**. These included dissection of left iliac artery, dissection of left circumflex and obtuse marginal arteries treated with stents, allergic reaction to platelets treated with an antihistamine agent and steroids, minor groin hematoma (2 patients), and minor dissection of right external iliac artery that was treated conservatively (no luminal obstruction; no vascular occlusion device used).

SE as a Screening Tool; Pre-CATH Stress Testing

The number of patients who underwent stress testing followed by CATH was 534 (66%), of these 515 (96%) patients had SE testing and 19 (4%) patients had nuclear stress testing **(Figure 1)**. Of the patients who had SE, 63 (12%) were positive, 404 (78%) were negative, and 48 (9%) were equivocal. Of note, 1 patient had positive CATH but initial stress testing was deferred. Of the patients who had nuclear testing, 3 (16%) had a positive test (1 patient had positive CATH) and 16 (84%) had a negative test (4 patients had positive CATH). Of the 48 patients who had equivocal SE, 8 (16%) patients had a positive CATH.

The number of patients who had a normal initial stress test not followed by CATH was 214 patients (28%), whereas 420 were followed by CATH (55%) (404 SE and 16 nuclear stress tests) **(Figure 1)**. CATH was normal

in 238 (57%) of these patients, showed non-obstructive disease in 152 (36%) patients, and 30 (7%) patients had significant CAD and received intervention. The sensitivity of SE in detecting significant CAD requiring intervention was found to be 37% **(Table 4)**. In other words, 63% of patients who received coronary intervention had a negative screening SE.

Pre- and Post-CATH Laboratory Values, Transfusions, and Acute Kidney Injury

The mean laboratory values were obtained for all 559 patients who underwent CATH within 1 day prior to CATH. Mean hemoglobin was 11.4±2.0 g/dL, mean INR 1.5±0.4, mean platelet count 89.9±60.7 × 10^9/L, and mean creatinine 1.2±1.1 mg/dL. No major bleeding events were recorded while minor bleeding events occurred in 14 patients (2.5%). A total of 10 patients (1.8%) received packed red blood cell transfusions pre-CATH and 12 patients (2.1%) post-CATH; 78 patients (14.0%) received platelet transfusions pre-CATH and 30 patients (5.3%) post-CATH; 183 patients (2.3%) received fresh frozen plasma and/or prothrombin complex concentrate pre-CATH and 82 patients (14.7%) post-CATH. Acute kidney injury was present in 24 patients (4.3%) up to 7 days post-CATH. Resolution of acute kidney injury occurred prior to discharge in 22 of the 24 patients, one of whom required temporary renal replacement therapy. The remaining 2 patients with no resolution of acute kidney injury were followed up by the outpatient nephrology service. One patient required intermittent hemodialysis with complete recovery while the other was diagnosed with hepatorenal syndrome and later underwent renal transplantation.

Cumulative Survival and Postoperative Cardiovascular Events

The mean follow-up period was 55.9 months with a standard deviation of 29.1 months, while the median was 52.7 months with a range of (0-109.1) months. Unadjusted Kaplan-Meier plot from 7-year cumulative survival analysis was used to compare patients who had no pre-transplant CATH, had normal coronaries, non-obstructive CAD, and significant CAD requiring intervention (Figure 3). Over time, the likelihood of surviving was lowest for those with severe CAD requiring intervention. The log rank test indicated that there were more estimated deaths in the CATH groups (normal, non-obstructive, severe) compared to the group with no indication for CATH (reference group), though not statistically significant (p=0.07). In the age-adjusted Cox proportional hazards model, the hazard rates (HR) of mortality increased with the severity of CAD compared

to those with no indication for CATH [CATH normal (HR: 1.35 [95% CI: 0.79, 2.33], p=0.298); non-obstructive CAD (HR: 1.53 [95% CI: 0.84, 2.77], p=0.161); severe CAD requiring intervention (HR: 1.96 [95% CI: 0.93, 4.15], p=0.080)].

There were 64 total deaths at 1 year post-LT. There were 6 MI events at 1 year (3 in the normal CATH group, 2 in the non-obstructive group, and 1 in the severe CAD group), of which 2 were fatal (1 in the normal CATH group and 1 in the non-obstructive group). In comparison, there were 11 deaths and 1 fatal MI event at 1 year in the 2009-2010 cohort. Hence, post-LT 1-year MI mortality and overall 1-year mortality in this study were comparable to the 2009-2010 cohort in the previous study who were managed using the same protocol (3% vs. 9% (of deaths) [p=0.35] and 8% vs. 6% (of all patients) [p=0.48], respectively) **(Figure 4)**.

The average timing for the incidence of cardiovascular event, indicated by elevated troponin, was 10 days post-transplant with a median of 4 days. The average peak troponin was 0.54 ng/ml and the median was 0.24 ng/ml. Cardiology team was consulted on 25 patients based on clinical symptoms, EKG changes, or increasing troponin values. Troponin was found to be elevated in setting of acute coronary syndrome, arrhythmias (atrial fibrillation, atrial flutter, and bradycardia with pauses), angiographically-proven coronary spasm, pericarditis, demand ischemia and stress cardiomyopathy in context of acute illness or profound anemia or shock requiring the use of vasopressors.

Discussion

Historically, it was thought that patients with end-stage liver disease are at lower risk of developing CAD as a result of hemodynamic and hormonal imbalances, as well as abnormal hepatic synthetic function seen in cirrhosis (11, 12). However, recent studies have shown that the prevalence of CAD in LT patients is equal to or greater than the general population (13, 14). Carey et al. evaluated 37 patients over age 50 awaiting LT with coronary angiography. Moderate CAD was defined as 30-70% stenosis, while severe CAD was defined as ≥70% stenosis, and the overall frequency of severe CAD was found to be 16% (15). Patients without risk factors were found to have significantly less CAD regardless of the type of liver disease, and diabetes was the most

important risk factor for moderate or severe CAD. Another study evaluated 161 patients over age 45 with angiography as part of LT evaluation and found that the prevalence of moderate (50% to 70%) to severe (>70%) CAD was 26% (14). The patients were more likely to be men and have hypertension or diabetes mellitus. Results from the present study show that significant CAD (≥50% stenosis in a major vessel warranting intervention) occurred in 10% of patients who underwent CATH or 7% of the total study population of 811 patients. Presence of CAD in this study was significantly associated with increasing age, male gender, personal history of CAD, diabetes mellitus and hypertension. These were all factors included in the risk factor screening adopted by our center in 2009, with the addition of smoking history, family history of CAD, and obesity. Results from this study suggest that these factors constitute an appropriate list for screening in this population.

Pre-transplant echocardiographic findings have yielded conflicting results with regards to predicting post-transplant morbidity and mortality (16-18). When stress tests were used as primary screening tools, they had low sensitivity and positive predictive value for asymptomatic patients, rendering them ineffective tools for this purpose (1, 19-21). In addition, higher MI rates were noted when dobutamine SE was the primary screening test in our center (9). The sensitivity and specificity of SE in detecting significant angiographically-proven CAD were calculated in our study as 37% and 89%, respectively. In comparison, Harinstein et al. found the sensitivity to be 13%, with comparable specificity of 85% in a total of 105 patients (22). These results suggest that SE is a poor screening test for CAD in LT candidates. The low sensitivity, or high false-negative event rate, may be due to inadequate response of beta-receptors to sympathetic stimulation in cirrhotic patients and/or concomitant use of beta-blockers for variceal bleeding prophylaxis, reducing the ability to reach target heart rates and subsequent induction of WMA with adequate stress levels (6).

Coronary computed tomography angiography (CCTA) may be an acceptable alternative to CATH in patients with low risk of CAD (1). However, its quality is affected by patient's clinical and physical status and it has poor positive predictive value of detecting significant CAD requiring revascularization (1, 23-25). Further studies are needed to evaluate the role of CCTA in detecting CAD in LT population, since to this date, there have been no reports comparing CCTA to CATH and the current studies included relatively small sample sizes. It is important to note that patients with renal dysfunction were excluded in these studies and the contrast

volume used was not reported. The amount of contrast used for CCTA is center-dependent; a typical CCTA requires 90-120 mL of iodine contrast (26). Therefore, it might not be a good alternative for patients with renal dysfunction in whom a diagnostic CATH may be performed with a lower amount of contrast.

Coronary angiography has been increasingly utilized to screen for CAD among LT candidates. However, this practice is not currently endorsed by American Heart Association/American College of Cardiology Foundation or American Association for the Study of Liver Diseases guidelines and remains center-specific. Multiple studies have analyzed the effect of revascularization on post-transplant survival. A small study of 47 LT patients who underwent CATH as part of pre-transplant workup found that the presence of multivessel CAD was associated with decreased survival following transplantation, even in the absence of severe coronary artery stenosis, suggesting that coronary angiography before transplantation may have a prognostic value. Notably, only 2 of these patients underwent revascularization (27). Among 630 patients undergoing pre-LT CATH in a multicenter cohort study over a 12-year period, there was no significant difference in 1-year survival between patients with obstructive CAD (≥50% stenosis) of whom 53% were revascularized, and those without obstructive CAD (28). Satapathy et al. reported on 87 LT recipients and found that survival in patients who underwent CATH, with revascularization when indicated, was comparable to those presumed not to have CAD based on non-invasive testing (29). In our study, patients who had an indication for CATH had lower 7-year survival as compared to those who did not undergo CATH (reference group), regardless of the CATH results. This indicates that the presence of certain risk factors could be an important determinant of long-term survival. It is important to note that mortality in this study did increase with the severity of CAD, while there was no significant difference in survival between the normal CATH, non-obstructive CAD, and obstructive CAD (revascularized) groups compared to the reference group ($p=0.30$, $p=0.16$, and $p=0.08$, respectively). This finding is likely related to the small sample size in these subgroups.

The rate of MI in our center is lower than what was previously reported in the literature. The MI rate during a median follow-up of 4 years was 2.8% in a German cohort of 352 LT patients that were screened per published guidelines (30). It is also lower than what was previously published in a review paper by Ali et al. comparing eight studies that used different screening modalities (31). Moreover, patients in the significant CAD group of our study only had 1 non-fatal MI. In addition, their survival at 7 years was less than 10% lower

than patients with no CAD. Therefore, patients with significant CAD requiring intervention have reasonable long-term outcomes and should not be excluded if they are otherwise good candidates for LT.

Patients with end-stage liver disease are more prone to CATH-related complications due to thrombocytopenia, anemia, coagulopathy, and kidney disease. Hence, they are at a higher risk of major bleeding, are more likely to require transfusions after CATH, and are at a higher risk of vascular complications such as pseudoaneurysms (32). In our study, 6 (1%) patients experienced immediate CATH-related complications. All cases were done using the femoral approach. Recently, a consensus published by the American Transplant Society recommended a radial approach in patients undergoing LT evaluation to improve hemostasis and reduce periprocedural complications (1). However, it is worth mentioning that our study (1/2010-12/2016) took place prior to the published consensus in 1/2018. In addition, the aforementioned recommendation favoring radial approach was based on 2 retrospectives studies. The first study by Huded et al. compared the rate of vascular and bleeding complications in a sample of 1071 patients (10% LT candidates, 90% non-LT candidates) undergoing CATH by radial approach (33). The study showed no difference in the rate of complications between the two groups. However, it does not directly compare radial and femoral approaches. Similarly, in the second study by Jacobs et al. radial CATH was performed in 82 patients with end-stage liver disease (34). Authors found this approach to be safe in LT candidates but again did not directly compare outcomes with the femoral approach. The RIVAL trial was the first large trial comparing radial versus femoral access for PCI in patients with acute coronary syndrome (35). There was no statistical difference in the primary outcome of a composite of death, MI, stroke or major bleeding between the two arms of the trial. There were significantly fewer vascular complications in the radial access group with respect to hematomas and pseudoaneurysms needing closure. However, it is important to note that the rate of major vascular complications with the radial approach was not superior to the femoral approach at high-volume femoral centers. A similar observation can be seen in the MATRIX trial, the largest randomized trial comparing radial versus femoral access in acute coronary syndrome (36). The rate of net adverse clinical events were similar between the radial and femoral groups at centers using predominantly femoral access, but the rate was higher at centers using predominantly radial access. Furthermore, a recent meta-analysis of randomized controlled trials in acute coronary syndrome suggests that the reported differences between the radial versus femoral approach may have been driven by adverse events in the femoral groups rather than beneficial effects of the radial approach (37). To date, there is no study that compares the two approaches in

the LT population. Based on the aforementioned data, the patient population and operator's experience might be more important for outcomes than the access site. The femoral technique used in our center was performed by an experienced single operator who used combined fluoroscopic and Doppler ultrasound guidance for optimal common femoral artery access in all cases, closure devices in more than 95% of the cases to reduce bleeding complications, and took appropriate precautions with reversing coagulopathies as necessary. Access site management in the RIVAL and MATRIX trials were left to the operator's discretion; the use of ultrasound was not mandated, and only 25.6% use of closure devices was reported in the RIVAL trial. Our center's technique did not result in any major bleeding events and in a minor bleeding incidence of only 2.5%. Another point is that with radial access, in addition to using vasodilating agents, 2500-5000 units of intra-arterial heparin or up to 100 IU/Kg is used to prevent thrombus formation after the wire is inserted that may lead to radial artery occlusion (38). Heparin is not needed in the femoral approach unless PCI is required. This is important to consider in the LT population where the risk of bleeding is already high due to coagulopathy.

CATH can be considered a safe procedure in LT patients (9, 32). However, it should be acknowledged that risk stratification by using a combination of risk factors may be a valuable tool that could allow for more selective use of CATH. As above, presence of CAD in our study was significantly associated with increasing age, male gender, personal history of CAD, hypertension, and diabetes mellitus. These results support a protocol of aggressive CAD screening with CATH based on risk factors and a lower threshold for coronary intervention, as it is associated with low cardiac morbidity and mortality.

We acknowledge the limitations of a retrospective study including the availability of test results, and reliability of clinical documentation and data collection. Also, our data represents a single center's transplant population which might differ from other centers. However, this might contribute to the strength of this study in having a single CATH operator and a strict protocol for patient selection and performing CATH. The rates of MI and mortality are likely underestimated in this cohort due to the retrospective design and reliance on available data. Additionally, delayed complications of CATH were not surveyed. Lastly, since this study only focuses on the preoperative LT evaluation, data collection pertaining to CAD for patients who were evaluated for, but did not undergo LT, was not performed.

Conclusion

This study shows that SE may not be a reliable screening tool for CAD in LT patients. The reported results serve as a validation of the previously published protocol by showing comparable outcomes of low rate of MI and cardiac mortality with aggressive CAD screening when extrapolated over a larger sample and longer follow-up period. Therefore, patients with significant CAD requiring intervention have reasonable long-term outcomes and should not be excluded if they are otherwise good candidates for LT.

References

1. VanWagner LB, Harinstein ME, Runo JR, Darling C, Serper M, Hall S, Kobashigawa JA, et al. Multidisciplinary approach to cardiac and pulmonary vascular disease risk assessment in liver transplantation: An evaluation of the evidence and consensus recommendations. Am J Transplant 2018;18:30-42.

2. Martin P, DiMartini A, Feng S, Brown R, Jr., Fallon M. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Hepatology 2014;59:1144-1165.

3. Lentine KL, Costa SP, Weir MR, Robb JF, Fleisher LA, Kasiske BL, Carithers RL, et al. Cardiac disease evaluation and management among kidney and liver transplantation candidates: a scientific statement from the American Heart Association and the American College of Cardiology Foundation: endorsed by the American Society of Transplant Surgeons, American Society of Transplantation, and National Kidney Foundation. Circulation 2012;126:617-663.

4. Pisano G, Fracanzani AL, Caccamo L, Donato MF, Fargion S. Cardiovascular risk after orthotopic liver transplantation, a review of the literature and preliminary results of a prospective study. World J Gastroenterol 2016;22:8869-8882.

5. Hogan BJ, Gonsalkorala E, Heneghan MA. Evaluation of coronary artery disease in potential liver transplant recipients. Liver Transpl 2017;23:386-395.

6. Kwon HM, Hwang GS. Cardiovascular dysfunction and liver transplantation. Korean J Anesthesiol 2018;71:85-91.

7. Neal DA, Tom BD, Luan J, Wareham NJ, Gimson AE, Delriviere LD, Byrne CD, et al. Is there disparity between risk and incidence of cardiovascular disease after liver transplant? Transplantation 2004;77:93-99.

8. De Lima JJ, Sabbaga E, Vieira ML, de Paula FJ, Ianhez LE, Krieger EM, Ramires JA. Coronary angiography is the best predictor of events in renal transplant candidates compared with noninvasive testing. Hypertension 2003;42:263-268.

9. Maddur H, Bourdillon PD, Liangpunsakul S, Joseph Tector A, Fridell JA, Ghabril M, Lacerda MA, et al. Role of cardiac catheterization and percutaneous coronary intervention in the preoperative assessment and management of patients before orthotopic liver transplantation. Liver Transpl 2014;20:664-672.

10. Pellikka PA, Nagueh SF, Elhendy AA, Kuehl CA, Sawada SG, American Society of E. American Society of Echocardiography recommendations for performance, interpretation, and application of stress echocardiography. J Am Soc Echocardiogr 2007;20:1021-1041.

11. Fede G, Privitera G, Tomaselli T, Spadaro L, Purrello F. Cardiovascular dysfunction in patients with liver cirrhosis. Ann Gastroenterol 2015;28:31-40.

12. Plevak DJ. Stress echocardiography identifies coronary artery disease in liver transplant candidates. Liver Transpl Surg 1998;4:337-339.

13. Kalaitzakis E, Rosengren A, Skommevik T, Bjornsson E. Coronary artery disease in patients with liver cirrhosis. Dig Dis Sci 2010;55:467-475.

14. Tiukinhoy-Laing SD, Rossi JS, Bayram M, De Luca L, Gafoor S, Blei A, Flamm S, et al. Cardiac hemodynamic and coronary angiographic characteristics of patients being evaluated for liver transplantation. Am J Cardiol 2006;98:178-181.

15. Carey WD, Dumot JA, Pimentel RR, Barnes DS, Hobbs RE, Henderson JM, Vogt DP, et al. The prevalence of coronary artery disease in liver transplant candidates over age 50. Transplantation 1995;59:859-864.

16. Bushyhead D, Kirkpatrick JN, Goldberg D. Pretransplant echocardiographic parameters as markers of posttransplant outcomes in liver transplant recipients. Liver Transpl 2016;22:316-323.

17. Batra S, Machicao VI, Bynon JS, Mehta S, Tanikella R, Krowka MJ, Zacks S, et al. The impact of left ventricular hypertrophy on survival in candidates for liver transplantation. Liver Transpl 2014;20:705-712.

18. Leithead JA, Kandiah K, Steed H, Gunson BK, Steeds RP, Ferguson JW. Tricuspid regurgitation on echocardiography may not be a predictor of patient survival after liver transplantation. Am J Transplant 2014;14:2192-2193.

19. Grande-Trillo A, Sobrino-Marquez JM, Escobedo-Mesas E, Rangel-Sousa D, Lopez-Haldon JE, Lage-Galle E. Preoperative Cardiac Assessment of Patients Undergoing Orthotopic Liver Transplantation: Experience in One Center. Transplant Proc 2015;47:2634-2635.

20. Nicolau-Raducu R, Gitman M, Ganier D, Loss GE, Cohen AJ, Patel H, Girgrah N, et al. Adverse cardiac events after orthotopic liver transplantation: a cross-sectional study in 389 consecutive patients. Liver Transpl 2015;21:13-21.

21. Aydinalp A, Bal U, Atar I, Ertan C, Aktaş A, Yildirir A, Ozin B, et al. Value of stress myocardial perfusion scanning in diagnosis of severe coronary artery disease in liver transplantation candidates. Transplant Proc 2009;41:3757-3760.

22. Harinstein ME, Flaherty JD, Ansari AH, Robin J, Davidson CJ, Rossi JS, Flamm SL, et al. Predictive value of dobutamine stress echocardiography for coronary artery disease detection in liver transplant candidates. Am J Transplant 2008;8:1523-1528.

23. Keeling AN, Flaherty JD, Davarpanah AH, Ambrosy A, Farrelly CT, Harinstein ME, Flamm SL, et al. Coronary multidetector computed tomographic angiography to evaluate coronary artery disease in liver transplant candidates: methods, feasibility and initial experience. J Cardiovasc Med (Hagerstown) 2011;12:460-468.

24. Cassagneau P, Jacquier A, Giorgi R, Amabile N, Gaubert JY, Cohen F, Muller C, et al. Prognostic value of preoperative coronary computed tomography angiography in patients treated by orthotopic liver transplantation. Eur J Gastroenterol Hepatol 2012;24:558-562.

25. Kemmer N, Case J, Chandna S, Neff GW. The role of coronary calcium score in the risk assessment of liver transplant candidates. Transplant Proc 2014;46:230-233.

26. Garcia MJ, Lessick J, Hoffmann MH, Investigators CS. Accuracy of 16-row multidetector computed tomography for the assessment of coronary artery stenosis. JAMA 2006;296:403-411.

27. Yong CM, Sharma M, Ochoa V, Abnousi F, Roberts J, Bass NM, Niemann CU, et al. Multivessel coronary artery disease predicts mortality, length of stay, and pressor requirements after liver transplantation. Liver Transpl 2010;16:1242-1248.

28. Wray C, Scovotti JC, Tobis J, Niemann CU, Planinsic R, Walia A, Findlay J, et al. Liver transplantation outcome in patients with angiographically proven coronary artery disease: a multi-institutional study. Am J Transplant 2013;13:184-191.

29. Satapathy SK, Vanatta JM, Helmick RA, Flowers A, Kedia SK, Jiang Y, Ali B, et al. Outcome of Liver Transplant Recipients With Revascularized Coronary Artery Disease: A Comparative Analysis With and Without Cardiovascular Risk Factors. Transplantation 2017;101:793-803.

30. Darstein F, Hoppe-Lotichius M, Vollmar J, Weyer-Elberich V, Zimmermann A, Mittler J, Otto G, et al. Pretransplant coronary artery disease is a predictor for myocardial infarction and cardiac death after liver transplantation. Eur J Intern Med 2018;51:41-45.

31. Ali A, Bhardwaj HL, Heuman DM, Jovin IS. Coronary events in patients undergoing orthotopic liver transplantation: perioperative evaluation and management. Clin Transplant 2013;27:E207-215.

32. Sharma M, Yong C, Majure D, Zellner C, Roberts JP, Bass NM, Ports TA, et al. Safety of cardiac catheterization in patients with end-stage liver disease awaiting liver transplantation. Am J Cardiol 2009;103:742-746.

33. Huded CP, Blair JE, Sweis RN, Flaherty JD. Transradial cardiac catheterization in liver transplant candidates. Am J Cardiol 2014;113:1634-1638.

34. Jacobs E, Singh V, Damluji A, Shah NR, Warsch JL, Ghanta R, Martin P, et al. Safety of transradial cardiac catheterization in patients with end-stage liver disease. Catheter Cardiovasc Interv 2014;83:360-366.

35. Jolly SS, Yusuf S, Cairns J, Niemela K, Xavier D, Widimsky P, Budaj A, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. Lancet 2011;377:1409-1420.

36. Valgimigli M, Frigoli E, Leonardi S, Vranckx P, Rothenbuhler M, Tebaldi M, Varbella F, et al. Radial versus femoral access and bivalirudin versus unfractionated heparin in invasively managed patients with acute coronary syndrome (MATRIX): final 1-year results of a multicentre, randomised controlled trial. Lancet 2018;392:835-848.

37. Shah R, Askari R, Haji SA, Rashid A. Mortality and operator experience with vascular access for percutaneous coronary intervention in patients with acute coronary syndromes: A pairwise and network meta-analysis of randomized controlled trials. Int J Cardiol 2017;248:114-119.

38. Hahalis GN, Leopoulou M, Tsigkas G, Xanthopoulou I, Patsilinakos S, Patsourakos NG, Ziakas A, et al. Multicenter Randomized Evaluation of High Versus Standard Heparin Dose on Incident Radial Arterial Occlusion After Transradial Coronary Angiography: The SPIRIT OF ARTEMIS Study. JACC Cardiovasc Interv 2018;11:2241-2250.

Figure Legends

Figure 1: Consort diagram representing 811 out of 3611 candidates who underwent LT with the pre-LT testing and their corresponding results. LT=liver transplant, CATH=cardiac catheterization, echo=echocardiogram.

Figure 2: Cardiac risk factors of patients who had negative CATH (no intervention) compared to patients who had positive CATH (CAD ≥50% stenosis in a major vessel or ≥70% stenosis in at least a moderate-sized branch vessel requiring intervention with PCI +/- balloon angioplasty). CATH=cardiac catheterization, BMI=body mass index, HTN on meds=hypertension on medications, Hx of CAD=history of coronary artery disease, PY=pack-years.

Figure 3: Unadjusted Kaplan-Meier plot from 7-year cumulative survival analysis for patients who had no pre-transplant cardiac catheterization (CATH), had normal coronaries, non-obstructive coronary artery disease (CAD), and significant CAD requiring intervention. Over time, the likelihood of surviving was lowest for those with severe CAD requiring intervention. The log-rank test indicated that there were more estimated deaths in the catheterization groups (normal, non-obstructive, severe) compared to the group with no indication for catheterization (reference group), though not statistically significant (p=0.07). In the age-adjusted Cox proportional hazards model, the hazard rates (HR) of mortality increased with the severity of CAD compared to those with no indication for CATH [CATH normal (HR: 1.35 [95% CI: 0.79, 2.33], p=0.298); non-obstructive CAD (HR: 1.53 [95% CI: 0.84, 2.77], p=0.161); severe CAD requiring intervention (HR: 1.96 [95% CI: 0.93, 4.15], p=0.080)].

Figure 4: Comparison between our current study (2010-2016) and a time period from our previous study (2009-2010) using the same protocol. The percentage of catheterization, intervention, 1-year mortality, MI within 1 year, and 1-year MI deaths (as portion of all deaths) was comparable between the 2 cohorts. MI=myocardial infarction.

Table 1. Demographics for 811 patients who underwent liver transplant.

	Number (%)
OVERALL	**811 (100%)**
MELD score	
20 or less	374 (46%)
21 to 29	351 (43%)
30 and higher	86 (11%)
Gender	
Male	546 (67%)
Female	265 (33%)
Race	
White	723 (89%)
Black	44 (5%)
Other	44 (5%)
Age (years)	
Less than 30	31 (4%)
30 to 39	39 (5%)
40 to 49	112 (14%)
50 to 59	317 (39%)
60 and older	312 (38%)
Body mass index (kg/m^2)	
Less than 25.0	218 (27%)
25.0 to 29.9	268 (33%)
30.0 to 34.9	219 (27%)
35.0 and higher	106 (13%)
Graft number	
First	786 (97%)
Re-transplant	25 (3%)
Etiology of Cirrhosis*	
Hepatitis C	267 (30%)
Alcohol	200 (22%)
NASH	179 (20%)
PSC	79 (9%)
Autoimmune	35 (4%)
PBC	34 (4%)
Cryptogenic	22 (2%)
Other	77 (9%)
Cardiac risk factors	

Diabetes mellitus	
No	565 (70%)
Yes	246 (30%)
Hypertension	
No	491 (61%)
Yes	320 (39%)
Tobacco	
Never	402 (50%)
Current (at evaluation)	126 (16%)
Former	283 (35%)
Tobacco pack years	
None	402 (50%)
1 to 20	223 (27%)
20 to 40	132 (16%)
>40	54 (7%)
Patient history of coronary artery disease	
No	756 (93%)
Yes	55 (7%)
Family history of coronary artery disease†	
None	466 (58%)
Immediate family (any)	296 (37%)
Distant family only	46 (6%)

MELD: Model for End-stage Liver Disease, NASH: Non-Alcoholic SteatoHepatitis, PSC: Primary Sclerosing Cholangitis, PBC: Primary Biliary Cirrhosis. * Many patients had more than one factor contributing to their liver disease; † 3 patients were adopted and did not have family history available.

Table 2. Results of pre-liver transplant cardiac stress testing in 766 patients who subsequently underwent liver transplant.

		Stress echocardiography results (n=742)					Nuclear stress results (n=24)		
	Underwent cardiac stress testing	Normal	Wall motion abnormalities	EKG changes without wall motion abnormalities	Non-diagnostic or equivocal	p-value	Normal nuclear test	Abnormal nuclear test	p-value
Number	**766/811 (94%)**	**613 (83%)**	**37 (5%)**	**26 (3%)**	**66 (9%)**		**21 (88%)**	**3 (13%)**	
RECIPIENT									
MELD score						0.38			0.45
20 or less	360	293 (48%)	17 (46%)	7 (27%)	29 (44%)		11 (52%)	3 (100%)	
21 to 29	331	263 (43%)	17 (46%)	15 (58%)	28 (42%)		8 (38%)	0 (0%)	
30 and higher	75	57 (9%)	3 (8%)	4 (15%)	9 (14%)		2 (10%)	0 (0%)	
Gender						0.10			>0.99
Male	516	402 (66%)	31 (84%)	17 (65%)	48 (73%)		16 (76%)	2 (67%)	
Female	250	211 (34%)	6 (16%)	9 (35%)	18 (27%)		5 (24%)	1 (33%)	
Race						0.61			>0.99
White	688	550 (90%)	34 (92%)	23 (88%)	58 (88%)		20 (95%)	3 (100%)	
Black	40	35 (6%)	1 (3%)	1 (4%)	2 (3%)		1 (5%)	0 (0%)	
Other	38	28 (5%)	2 (5%)	2 (8%)	6 (9%)		0 (0%)	0 (0%)	
Age (years)						0.18			0.18
Less than 30	22	20 (3%)	0 (0%)	0 (0%)	2 (3%)		0 (0%)	0 (0%)	
30 to 39	34	31 (5%)	0 (0%)	1 (4%)	2 (3%)		0 (0%)	0 (0%)	
40 to 49	108	84 (14%)	4 (11%)	4 (15%)	13 (20%)		3 (14%)	0 (0%)	
50 to 59	302	254 (41%)	13 (35%)	5 (19%)	24 (36%)		4 (19%)	2 (67%)	
60 and older	300	224 (37%)	20 (54%)	16 (62%)	25 (38%)		14 (67%)	1 (33%)	
Body mass index (kg/m^2)						0.11			>0.99
Less than 25.0	202	157	7 (19%)	5 (19%)	28 (42%)		5 (24%)	0 (0%)	

		(26%)							
		209							
25.0 to 29.9	256	(34%)	12 (32%)	12 (46%)	15 (23%)		7 (33%)	1 (33%)	
		165							
30.0 to 34.9	207	(27%)	14 (38%)	7 (27%)	16 (24%)		4 (19%)	1 (33%)	
35.0 and higher	101	82 (13%)	4 (11%)	2 (8%)	7 (11%)		5 (24%)	1 (33%)	
Graft number						0.36			*
		596							
First	745	(97%)	36 (97%)	24 (92%)	65 (98%)		21 (100%)	3 (100%)	
Re-transplant	21	17 (3%)	1 (3%)	2 (8%)	1 (2%)		0 (0%)	0 (0%)	
Cardiac risk factors									
						<0.00			>0.9
Diabetes mellitus						1			9
		444							
No	532	(72%)	15 (41%)	14 (54%)	44 (67%)		13 (62%)	2 (67%)	
		169							
Yes	234	(28%)	22 (59%)	12 (46%)	22 (33%)		8 (38%)	1 (33%)	
Hypertension						0.72			0.27
		368							
No	458	(60%)	21 (57%)	13 (50%)	41 (62%)		12 (57%)	3 (100%)	
		245							
Yes	308	(40%)	16 (43%)	13 (50%)	25 (38%)		9 (43%)	0 (0%)	
									>0.9
Tobacco						0.94			9
		304							
Never	378	(50%)	16 (43%)	15 (58%)	33 (50%)		9 (43%)	1 (33%)	
Current (at evaluation)	116	94 (15%)	5 (14%)	3 (12%)	11 (17%)		3 (14%)	0 (0%)	
		215							
Former	272	(35%)	16 (43%)	8 (31%)	22 (33%)		9 (43%)	2 (67%)	
									>0.9
Tobacco pack years						0.81			9
		304							
None	378	(50%)	16 (43%)	15 (58%)	33 (50%)		9 (43%)	1 (33%)	
		159							
1 to 20	209	(26%)	12 (32%)	6 (23%)	22 (33%)		8 (38%)	2 (67%)	
		103							
20 to 40	127	(17%)	7 (19%)	4 (15%)	9 (14%)		4 (19%)	0 (0%)	
>40	52	47 (8%)	2 (5%)	1 (4%)	2 (3%)		0 (0%)	0 (0%)	
Patient history of coronary artery disease						<0.00			>0.9

						1		9
		585						
No	714	(95%)	26 (70%)	22 (85%)	61 (92%)		17 (81%)	3 (100%)
Yes	52	28 (5%)	11 (30%)	4 (15%)	5 (8%)		4 (19%)	0 (0%)
Family history of coronary								
artery disease[†]						0.45		>0.9 9
		353						
None	434	(58%)	23 (62%)	15 (58%)	34 (52%)		8 (38%)	1 (33%)
Immediate family (any)	286	220 (36%)	14 (38%)	8 (31%)	29 (44%)		13 (62%)	2 (67%)
Distant family only	43	37 (6%)	0 (0%)	3 (12%)	3 (5%)		0 (0%)	0 (0%)

MELD: Model for End-stage Liver Disease. * Unable to calculate p-value because of small cell values; † 3 patients were adopted and did not have family history available.

Table 3. Results of pre-liver transplant cardiac catheterization in 559 patients who subsequently underwent liver transplant.

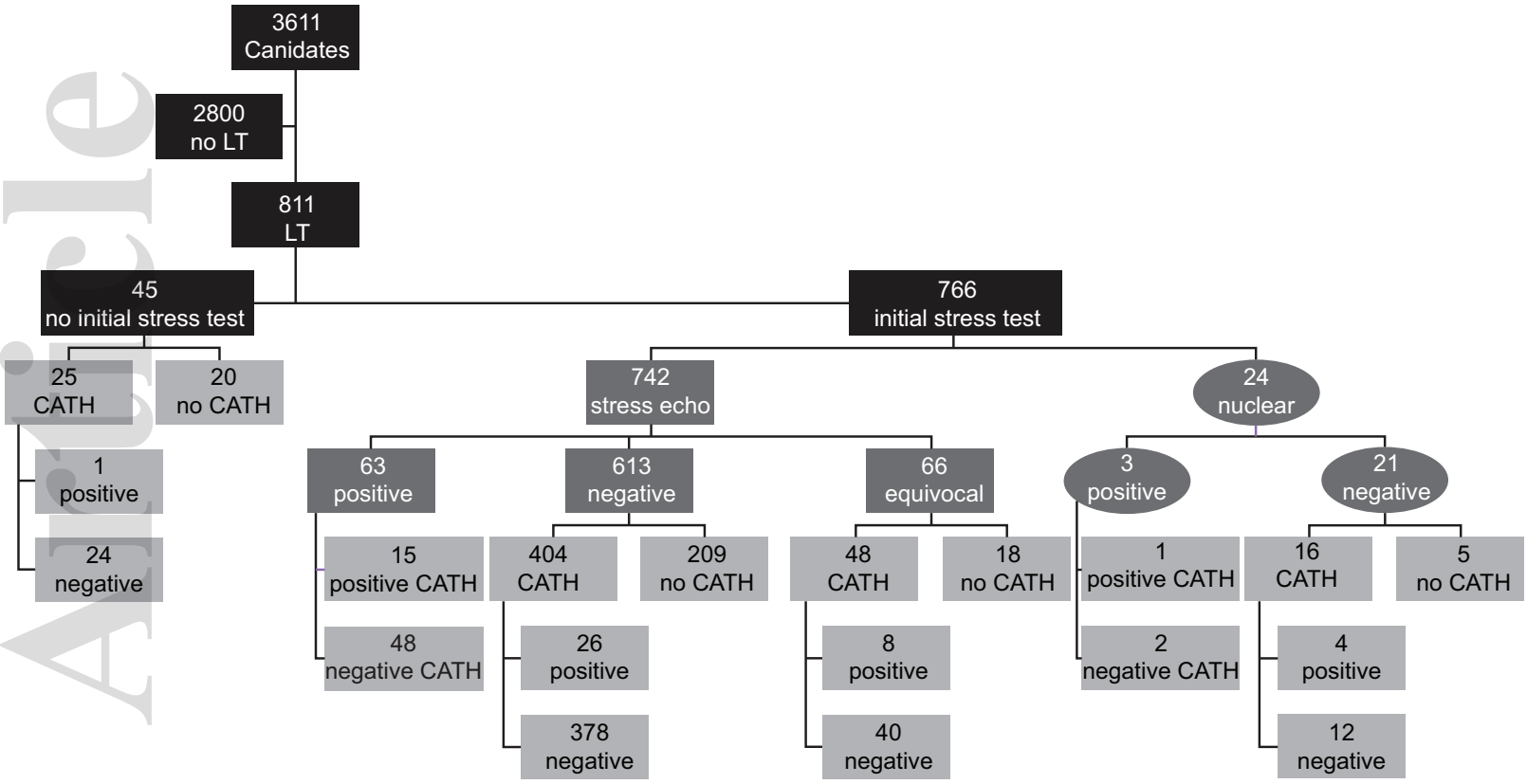
		Cardiac catheterization results					
	Underwent cardiac catheterization	Normal or no catheterization indicated	Non-obstructive coronary artery disease	Obstructive coronary artery disease requiring intervention	p-value	Complication of catheterization	p-value
Number	**559/811 (69%)**	**314 (56%)**	**190 (34%)**	**55 (10%)**		**6 (1%)**	
RECIPIENT							
MELD score					0.73		0.48
20 or less	264 (47%)	151 (48%)	91 (48%)	22 (40%)		2 (33%)	
21 to 29	247 (44%)	137 (44%)	84 (44%)	26 (47%)		4 (67%)	
30 and higher	48 (9%)	26 (8%)	15 (8%)	7 (13%)		0 (0%)	
Gender					<0.01		0.67
Male	391 (70%)	202 (64%)	141 (74%)	48 (87%)		5 (83%)	
Female	168 (30%)	112 (36%)	49 (26%)	7 (13%)		1 (17%)	
Race					0.81		0.29
White	509 (91%)	284 (90%)	173 (91%)	52 (95%)		5 (83%)	
Black	26 (5%)	15 (5%)	10 (5%)	1 (2%)		0 (0%)	
Other	24 (4%)	15 (5%)	7 (4%)	2 (4%)		1 (17%)	
Age (years)					<0.001		*
Less than 30	0 (0%)	0 (0%)	0 (0%)	0 (0%)		0 (0%)	
30 to 39	4 (1%)	3 (1%)	1 (1%)	0 (0%)		1 (17%)	
40 to 49	40 (7%)	30 (10%)	8 (4%)	2 (4%)		0 (0%)	
50 to 59	220 (39%)	145 (46%)	62 (33%)	13 (24%)		1 (17%)	
60 and older	295 (53%)	136 (43%)	119 (63%)	40 (73%)		4 (67%)	
Body mass index (kg/m^2)					0.22		*
Less than 25.0	127 (23%)	74 (24%)	36 (19%)	17 (31%)		2 (33%)	
25.0 to 29.9	189 (34%)	95 (30%)	77 (41%)	17 (31%)		1 (17%)	
30.0 to 34.9	161 (29%)	95 (30%)	51 (27%)	15 (27%)		3 (50%)	
35.0 and higher	82 (15%)	50 (16%)	26 (14%)	6 (11%)		0 (0%)	
Graft number					0.06		0.74
First	549 (98%)	311 (99%)	186 (98%)	52 (95%)		6 (100%)	
Re-transplant	10 (2%)	3 (1%)	4 (2%)	3 (5%)		0 (0%)	
Cardiac risk factors							
Diabetes mellitus					0.05		*
No	338 (60%)	204 (65%)	105 (55%)	29 (53%)		3 (50%)	
Yes	221 (40%)	110 (35%)	85 (45%)	26 (47%)		3 (50%)	
Hypertension					0.03		*

No	305 (55%)	187 (60%)	92 (48%)	26 (47%)		4 (67%)	
Yes	254 (45%)	127 (40%)	98 (52%)	29 (53%)		2 (33%)	
Tobacco					0.97		*
Never	221 (40%)	124 (39%)	75 (39%)	22 (40%)		1 (17%)	
Current (at evaluation)	107 (19%)	63 (20%)	35 (18%)	9 (16%)		3 (50%)	
Former	231 (41%)	127 (40%)	80 (42%)	24 (44%)		2 (33%)	
Tobacco pack years					1.00		*
None	221 (40%)	124 (39%)	75 (39%)	22 (40%)		1 (17%)	
1 to 20	164 (29%)	92 (29%)	57 (30%)	15 (27%)		3 (50%)	
20 to 40	123 (22%)	71 (23%)	40 (21%)	12 (22%)		2 (33%)	
>40	51 (9%)	27 (9%)	18 (9%)	6 (11%)		0 (0%)	
Patient history of coronary artery disease					<0.001		*
No	506 (91%)	307 (98%)	164 (86%)	35 (64%)		4 (67%)	
Yes	53 (9%)	7 (2%)	26 (14%)	20 (36%)		2 (33%)	
Family history of coronary artery disease[†]					0.25		*
None	300 (54%)	180 (57%)	96 (51%)	24 (44%)		3 (50%)	
Immediate family (any)	236 (42%)	123 (39%)	84 (44%)	29 (53%)		3 (50%)	
Distant family only	23 (4%)	11 (4%)	10 (5%)	2 (4%)		0 (0%)	

MELD: Model for End-stage Liver Disease. * Unable to calculate p-value because of small cell values; † 3 patients were adopted and did not have family history available.

Table 4. Utility of pre-liver transplant stress echocardiography testing in predicting coronary artery disease requiring intervention.

		Cardiac Catheterization		
		Positive	Negative	
Stress echocardiogram	Positive	15	48	63
	Negative	26	378	404
		41	426	467
	Sensitivity	15/41*100	37%	



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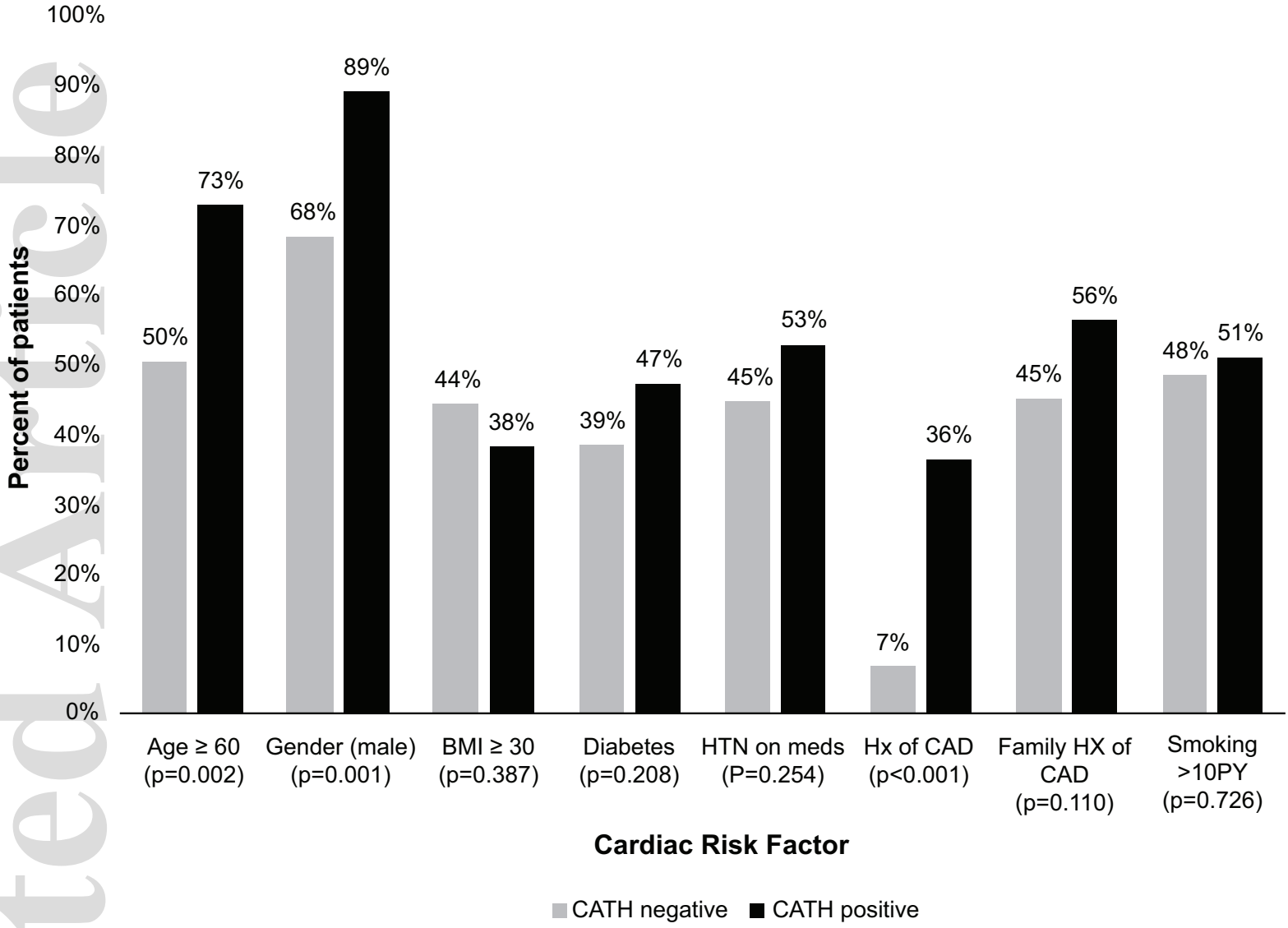

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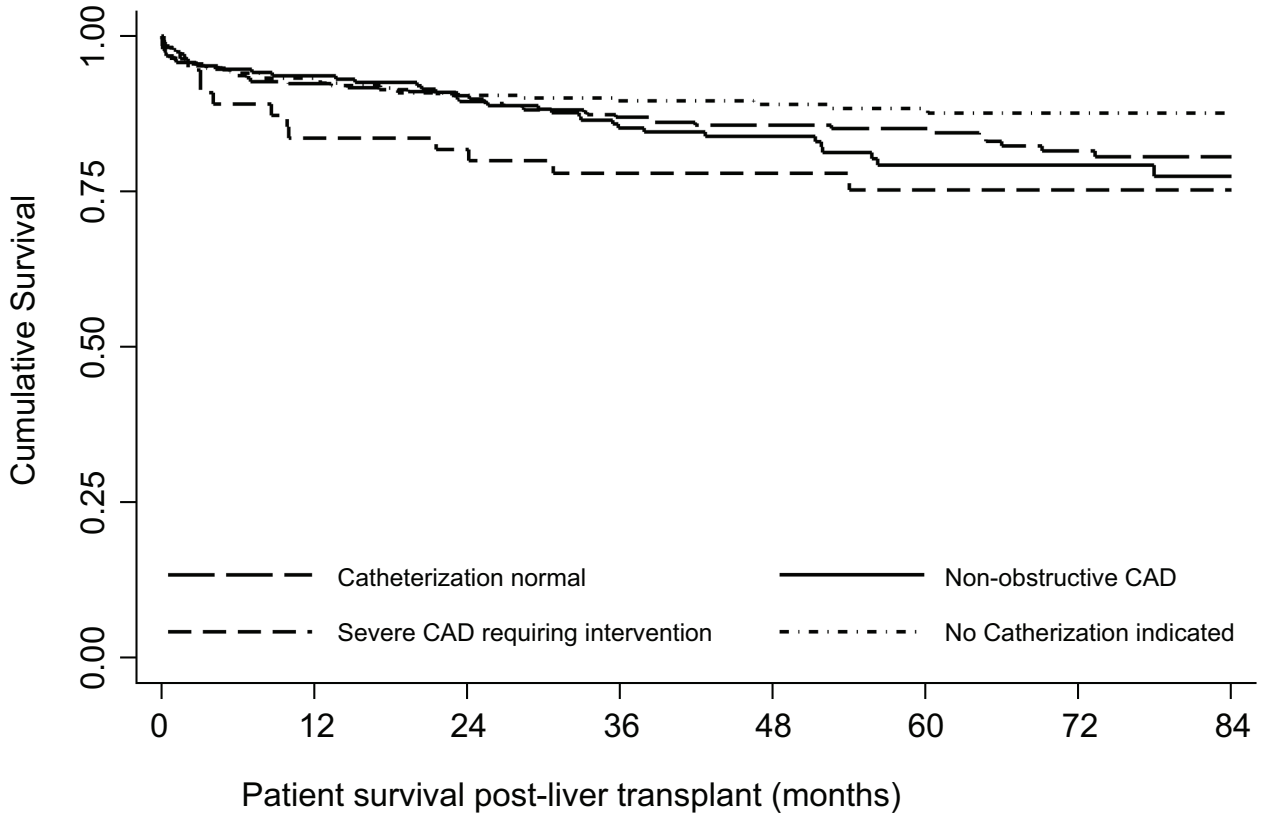

Number at risk

Catheterization normal	252	235	228	188	154	120	103	62
Non-obstructive CAD	188	176	170	136	105	69	54	31
Severe CAD requiring intervention	55	46	45	37	32	25	18	12
No Catherization indicated	314	290	281	217	168	129	93	64

p-value=0.07

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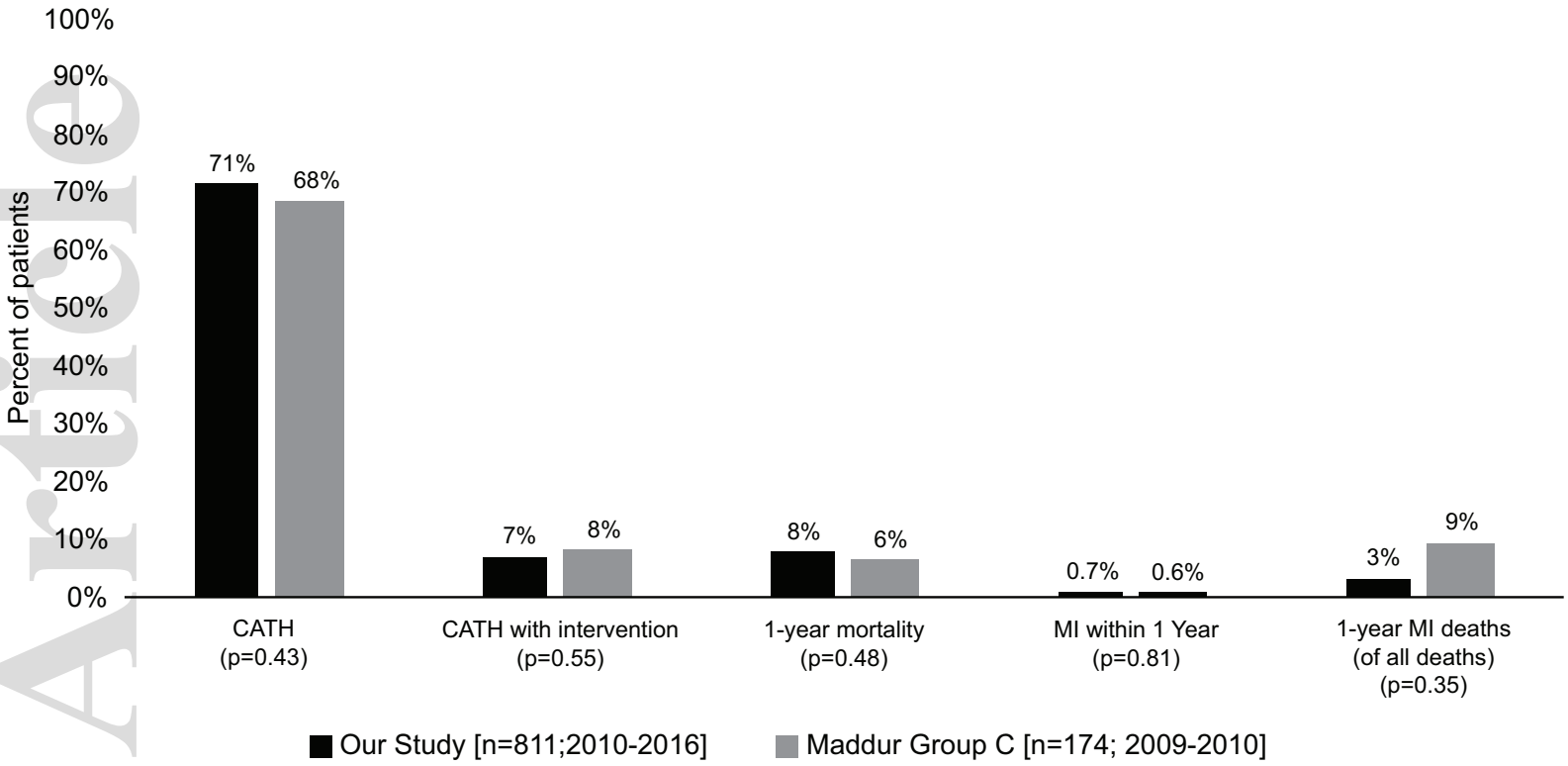

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