The Impact of Coronary Artery Disease and Statins on Survival After Liver Transplantation

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Cardiovascular disease (CVD) is a major contributor to longterm mortality after liver transplantation (LT) necessitating aggressive modification of CVD risk. However, it is unclear how coronary artery disease (CAD) and the development of dyslipidemia following LT impacts clinical outcomes and how management of these factors may impact survival. Patients undergoing LT at Virginia Commonwealth University from January 2007 to January 2017 were included (n = 495). CAD and risk factors in all potential liver transplantation recipients (LTRs) over the age of 50 years were evaluated via coronary angiography. The impact of pre-LT CAD after transplantation was evaluated via a survival analysis. Additionally, factors associated with new-onset dyslipidemia, statin use, and mortality were assessed using multiple logistic regression or Cox proportional hazards models. The mean age of the cohort was 55.3 ± 9.3 years at the time of LT, and median follow-up was 4.5 years. CAD was noted in 129 (26.1%) patients during the pre-LT evaluation. The presence or severity of pre-LT CAD did not impact post-LT survival. Dyslipidemia was present in 96 patients at LT, and 157 patients developed new-onset dyslipidemia after LT. Statins were underused as only 45.7% of patients with known CAD were on therapy. In patients with new-onset dyslipidemia, statin therapy was initiated in 111 (71.1%), and median time to initiation of statin therapy was 2.5 years. Statin use conferred survival benefit (hazard ratio, 0.25; 95% confidence interval, 0.12-0.49) and was well tolerated with only 12% of patients developing an adverse event requiring the cessation of therapy. In conclusion, pre-LT CAD did not impact survival after LT, potentially suggesting a role of accelerated atherosclerosis that may not be captured on pre-LT testing. Although statin therapy confers survival benefit, it is underused in LTRs.

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Cardiovascular disease (CVD) is an important contributor to longterm mortality following liver transplantation (LT).1-3 This fact in itself is not shocking because CVD-related mortality is the leading cause of morbidity and mortality in the United States.4 However, unlike the general population, all potential liver transplantation recipients (LTRs) undergo vigorous pre-LT testing aimed at identifying and eliminating individuals deemed to be “high risk” for perioperative and postoperative complications.5 The cardiac evaluation prior to LT generally includes a measure of cardiac function by echocardiography and an assessment of coronary artery disease (CAD). Patients with heart failure with a reduced ejection fraction are nearly universally excluded due to high intraoperative mortality.6 In contrast, although the practice for assessing for CAD is highly variable, patients with an abnormal CAD assessment undergo coronary angiography, which is the
gold standard for CAD assessment, and revascularization.\(^{(7)}\) Those who are unable to be revascularized are eliminated from further LT consideration. Since not all patients receiving a LT undergo coronary angiography, it is unclear if CVD and mortality following LT represent an exacerbation of nonobstructive CAD present at the time of LT or if they result from LTRs being at an increased risk for accelerated atherosclerosis.

The CVD risk is compounded further following LT because patients are at increased risk of developing dyslipidemia, which is an independent predictor of CVD mortality.\(^{(8)}\) There are several mechanisms of post-LT dyslipidemia including corticosteroids, chronic exposure to immunosuppression, weight gain, and development of nonalcoholic fatty liver disease.\(^{(9-13)}\) Prior studies have demonstrated that the prevalence of dyslipidemia is high following LT\(^{(8)}\) and varies significantly on the basis of the etiology of chronic liver disease.\(^{(1)}\) Post-LT dyslipidemia is characterized by an increase in highly atherogenic small-dense low-density lipoprotein, which is negatively affected by the type of immunosuppression and the presence of hepatic steatosis.\(^{(9,10)}\) Collectively, the presence of dyslipidemia and the increase in atherogenic lipoprotein translates clinically into increased morbidity and mortality following LT.\(^{(14)}\) However, the impact of dyslipidemia on the future risk of mortality and, more importantly, on the effect of clinically treating dyslipidemia remains poorly defined. To address these limitations within the field, we conducted the following study to link pre-LT CAD to post-LT mortality, evaluate the incidence rates of dyslipidemia, and describe the management of post-LT dyslipidemia and the associated impact on mortality.

Patients and Methods

All patients receiving an LT at Virginia Commonwealth University (VCU) were prospectively enrolled in a study evaluating post-LT outcomes, and the current study represents a retrospective analysis of this cohort. The substudy was reviewed and approved by the VCU institutional review board, and the manuscript was reviewed and approved by all authors prior to submission.

PATIENT POPULATION

The present analysis included all patients receiving a LT at VCU over a 10-year period between January 1, 2007, and January 1, 2017. Pre-LT CVD was assessed via echocardiography and either a cardiac stress test or a coronary angiography. A coronary angiography was performed in all patients age ≥50 years or who had the presence of risk factors (diabetes, hypertension, dyslipidemia, obesity, family history, smoking history, or personal history of CAD). Those without risk factors and age <50 years had a noninvasive cardiac stress test, and coronary angiography was reserved for those with an abnormal stress test. The severity and distribution of CAD were defined according to the Coronary Artery Surgery Study.\(^{(15)}\) The decision to intervene on coronary artery stenosis was made in a multidisciplinary approach as described previously.\(^{(7,16)}\) Pediatric patients undergoing LT were excluded. Additionally, patients who were not transplanted at VCU medical center and later translocated to VCU were excluded because their pre-LT cardiac evaluation was not readily available. The data were collected before LT, at the time of LT, and follow-up visits every 6 months. Unscheduled visits or hospitalizations were reviewed for all patients through a review of medical records.
DEFINITIONS AND CLINICAL OUTCOMES

Coronary assessment prior to LT included coronary angiography in patients over the age of 50 years, risk factors for CAD, and those with abnormal cardiac stress tests as described previously.(7,16) CAD noted during the LT evaluation was characterized based on the presence of any luminal stenosis of coronary arteries. CAD was further stratified as obstructive if there was >50% stenosis of any of the 3 major coronary vessels (right coronary artery, left anterior descending, or left circumflex artery).(15) Circulatory death was defined as death in the setting of myocardial infarction, ventricular arrhythmias, cardiogenic shock, or if the death was sudden and unexplained.(17)

Obesity was defined as body mass index ≥30 kg/m².(18) The presence of diabetes was defined as the use of diabetes medications, hemoglobin A1c >6.5%, or elevated serum glucose (fasting >126 mg/dL or random >200 mg/dL).(19) Hypertension was defined as the use of antihypertensive medications or systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥80 mm Hg.(20) Dyslipidemia was defined as 1 of the following:

1. Total cholesterol ≥200 mg/dL.
2. Low-density lipoprotein cholesterol (LDL-C) ≥100 mg/dL in diabetics.
3. LDL-C >130 mg/dL in nondiabetics.
4. High-density lipoprotein cholesterol (HDL-C) <40 mg/dL and 50 mg/dL in men and women, respectively.(21)

Patients were considered to have dyslipidemia if they met these laboratory criteria at any follow-up visit. Patients with a pretransplant diagnosis of dyslipidemia who remained on statin therapy were also considered to have dyslipidemia even if their lipid profile did not meet laboratory criteria. Guidelines to initiate and titrate lipid-lowering therapy have evolved over the course of the current study period.(21,22) Thus, to present data regarding statin use in this proof-of-concept study, an appropriate initiation of statin therapy was considered if (1) serum LDL-C >100 mg/dL in diabetics, (2) LDL-C >130 mg/dL in nondiabetics, or (3) total cholesterol >200 mg/dL.(21)

Finally, patients with a known history of CVD (myocardial infarction, CAD as documented on coronary angiography, or stroke) were considered to be eligible for statin therapy regardless of lipid profile.(23) Patients with CAD at LT and patients at increased risk for CVD events were considered eligible for aspirin therapy. Aspirin use and statin use were determined by reviewing clinical notes (eg, hepatology, primary care, transplant surgery, and endocrinology), as well as a review of the prescriptions filled at the pharmacy. In patients not on statin therapy, medical records were reviewed to evaluate the potential reasons for not initiating statin therapy. Adverse events linked to statin therapy included myositis, myalgias, rhabdomyolysis, rising serum transaminases (more than 3 times the upper limit of normal), and acute liver failure or injury, and they were quantified in the current study.(24)

STATISTICAL ANALYSIS

Mean and standard deviation (SD) or median and interquartile range (IQR) in the presence of highly skewed distributions and frequencies and percentages are reported for each study variable at baseline. The prevalence of dyslipidemia at LT and at 1, 3, and 5 years after LT is reported. Factors associated with dyslipidemia were assessed with logistic regression models built to obtain crude and adjusted odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) for age, sex, ethnicity, etiology of liver disease, obesity, hypertension, and diabetes. The generalized variance inflation factor was used to assess multicollinearity in the models. Cox proportional hazards models were built to evaluate the effect of the aforementioned variables on developing dyslipidemia after LT; crude and adjusted hazard ratios (HRs) with their 95% CIs were calculated. Locally estimated scatterplot smoothing curves of the lipid panel (triglycerides, HDL-C, LDL-C, and total cholesterol) were produced to evaluate the relationship between their pattern and the primary etiology of liver disease.

The pattern of statin use was described by reporting the proportions of users among those eligible for statin therapy at LT and at 1, 3, and 5 years after LT. Logistic regression models were used to assess the association with post-LT statin therapy eligibility and with post-LT statin therapy use. Crude and adjusted ORs and 95% CIs are reported. A Kaplan-Meier analysis was used to describe the time until eligibility for statin therapy and the time until statin therapy initiation. Additionally, linear mixed-effects models were used to estimate the average impact of statin therapy and time on the serum liver enzymes, adjusting for age, sex, diabetes, and etiology of liver disease. A Kaplan-Meier analysis was used to describe the survival time by statin therapy and by CAD presence.
Results

PATIENT CHARACTERISTICS

A total of 495 patients underwent LT at VCU between January 2007 and January 2017, and the pre-LT demographics of the study cohort are summarized in Table 1. The mean age at LT was 55.3 ± 9.3 years, and 72.3% were males. The most common etiology of chronic liver disease was hepatitis C virus (HCV; n = 227 or 45.9%), followed by alcohol-related cirrhosis (n = 79 or 16.0%), and nonalcoholic steatohepatitis (NASH; n = 78 or 15.8%). The prevalence of hypertension, diabetes, and obesity before LT was 48.5%, 30.5%, and 20.0%, respectively. The median follow-up period was 4.5 years (IQR, 2.4-5.0 years). Calcineurin inhibitors were the most commonly used immunosuppressants with tacrolimus serving as the main immunosuppressant in 347 (70%) LTRs and cyclosporine in 119 (24%) of patients. Sirolimus was used in only 29 (5.9%) of patients. Coronary angiography was performed in 424 of 495 patients. The prevalence of any CAD and obstructive CAD was 26.1% (n = 129) and 7.9% (n = 39), respectively. There were 22 patients who required revascularization prior to LT (Supporting Fig. 1).

DYSLIPIDEMIA

At the time of LT, 96 (20.3%) patients had a diagnosis of dyslipidemia. Patients with NASH had the highest prevalence (n = 35 or 36.5%), followed by alcohol-related cirrhosis (n = 15 or 15.6%) and HCV (n = 24 or 25.0%; P < 0.001). Factors associated with dyslipidemia prior to LT included older age, NASH as an indication for LT, diabetes, hypertension, and CAD (Table 2). In an adjusted model, older age (OR, 1.06; 95% CI, 1.01-1.11; P = 0.017), NASH as an indication for LT (OR, 2.95; 95% CI, 1.37-6.56; P = 0.007), and hypertension (OR, 2.05; 95% CI, 1.13-3.80; P = 0.020) remained significantly associated with a diagnosis of dyslipidemia (Table 2).

The prevalence of dyslipidemia at 1, 3, and 5 years after LT was 32.5% (n = 146), 46.8% (n = 142), and 55.3% (n = 115), respectively. There were 111 (22.4%) patients who were missing a lipid profile during the first 2 years after LT; however, of these patients, 40 died within 1 year after LT. No systematic differences were noted among patients who had a lipid profile performed within 2 years following LT and those who did not. In patients without CAD and dyslipidemia prior to LT, the annual incidence rates of dyslipidemia are depicted in Fig. 1. The median time from LT to developing dyslipidemia was 1.5 years (IQR, 0.5-3.0 years). The specific changes in serum total cholesterol,
TABLE 2. Association Between Clinical Characteristics and Dyslipidemia at the Time of LT

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Unadjusted OR (95% CI)</th>
<th>P Value</th>
<th>Adjusted* OR (95% CI)</th>
<th>P Value</th>
<th>Adjusted† OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.06 (1.03-1.10)</td>
<td>&lt;0.001</td>
<td>1.05 (1.00-1.10)</td>
<td>0.052</td>
<td>1.06 (1.01-1.11)</td>
<td>0.02</td>
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<tr>
<td>Male</td>
<td>1.04 (0.64-1.74)</td>
<td>0.86</td>
<td>1.10 (0.55-2.28)</td>
<td>0.79</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>1.00</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>African American</td>
<td>0.76 (0.43-1.30)</td>
<td>0.33</td>
<td>0.97 (0.43-2.08)</td>
<td>0.95</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>1.00</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>HCV</td>
<td>0.50 (0.25-1.02)</td>
<td>0.05</td>
<td>0.46 (0.22-0.98)</td>
<td>0.04</td>
<td>0.44 (0.21-0.93)</td>
<td>0.03</td>
</tr>
<tr>
<td>NASH</td>
<td>3.34 (1.66-7.00)</td>
<td>&lt;0.001</td>
<td>2.57 (1.14-5.92)</td>
<td>0.02</td>
<td>2.95 (1.37-6.56)</td>
<td>0.007</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.84 (1.78-4.63)</td>
<td>&lt;0.001</td>
<td>1.72 (0.93-3.24)</td>
<td>0.09</td>
<td>2.05 (1.13-3.80)</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.31 (1.46-3.65)</td>
<td>&lt;0.001</td>
<td>1.59 (0.86-2.91)</td>
<td>0.14</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>CAD</td>
<td>2.22 (1.38-3.54)</td>
<td>&lt;0.001</td>
<td>1.60 (0.87-2.90)</td>
<td>0.13</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*The following variables were included in the model: age, sex, ethnicity, etiology, obesity, hypertension, diabetes, and CAD.
†The following variables were included in the model: age, etiology, obesity, and hypertension.

LDL-C, HDL-C, and triglycerides are delineated in Supporting Figs. 2A-D and are stratified to the etiology of liver disease. Total cholesterol increased across all etiologies of chronic liver disease over time, but the rate of change was the greatest within the first 2 years following LT. Similarly, serum triglycerides also rapidly increased across etiologies of chronic liver disease with time with the greatest increase in slope occurring within the first 2 years following LT. The change in serum LDL-C and HDL-C were similar across the etiologies of chronic liver disease.

In the unadjusted analysis, factors associated with the development of dyslipidemia after LT included male sex, HCV as the indication for LT, hypertension, diabetes, and the presence of CAD. In the adjusted model, patients with HCV as the indication for LT were less likely to develop dyslipidemia after LT (HR, 0.54; 95% CI, 0.36-0.83; P = 0.004), whereas those with pre-LT CAD were more likely (HR, 1.56; 95% CI, 1.08-2.27; P = 0.019; Table 3).

**PATTERN OF STATIN AND ASPIRIN USE**

Prior to LT, only 14.5% (n = 16) with any CAD were on statin therapy, and the proportion of patients on statin was slightly higher in patients with obstructive CAD (n = 11 or 33.3%). After LT, 374 patients (75.6%) were eligible for statin therapy during the study period; however, only 46.8% (n = 175) of the eligible patients received statin therapy. In a deeper analysis of the patients eligible for statin therapy, 18.4% (n = 18) of the patients with any CAD were on statin therapy at 1 year, 45.7% (n = 32) at 3 years, and 40.0% (n = 12) at 5 years. In patients with obstructive CAD at LT who underwent revascularization, 50% were on statin therapy at 1 year.

In patients with new-onset dyslipidemia, median time to initiation of statin therapy from diagnosis of dyslipidemia was 2.5 years (IQR, 0.5-4.5 years; Fig. 2). Initiation of statin therapy following LT in patients with CAD is depicted in Fig. 2. The likelihood of initiating statin therapy was higher among diabetics (OR, 1.58; 95% CI, 1.00-2.51; P = 0.049)

![Cumulative probability of developing dyslipidemia](image)  
**FIG. 1.** The annual incidence rates of dyslipidemia after LT.
and African Americans (OR, 1.80; 95% CI, 1.05-3.09; *P* = 0.03). In contrast, males (OR, 0.45; 95% CI, 0.28-0.71; *P* < 0.001) and patients with HCV (OR, 0.46; 95% CI, 0.24-0.86; *P* = 0.02) were less likely to be started on statin therapy. Finally, LTRs started on statin therapy had lower aspartate transaminase (AST) values than eligible patients who did not start statin therapy (adjusted difference, 6.0 IU/mL; 95% CI, −3.1 to 15.1 IU/mL).

After initiation of statin therapy, 26.3% (n = 46) of patients did not have a follow-up lipid profile assessed within 2 years. In patients with a repeat lipid profile after initiation of statin therapy, 44.0% (n = 77) were adequately titrated to either high-dose statin therapy or goal LDL-C level. The intensity of statin therapy was increased in 5.7% (n = 10) of patients with a suboptimal reduction in serum LDL-C. Finally, the majority of LTRs started on statin therapy received moderate-intensity statin therapy (Fig. 3).

A total of 286 LTRs were eligible for aspirin therapy; however, only 117 (40.9%) LTRs were on aspirin during the study duration. In unadjusted and adjusted regression models, a history of hypertension was positively associated with aspirin utilization (OR, 1.91; 95% CI, 1.09-3.42; *P* = 0.03). African Americans and patients with NASH were more likely to use aspirin, which did not reach statistical significance (Supporting Table 1).

### ADVERSE EFFECTS ASSOCIATED WITH STATIN THERAPY

Statin therapy was interrupted in 53 (30.3%) patients. Of these, 28 (16.0%) had temporary discontinuation of statin therapy, whereas 4 (2.3%) patients stopped statin therapy due to medical noncompliance without a reported adverse event. There were 21 (12.0%) patients who had a documented adverse event related to statin therapy, and muscle-related complications were the most common complication occurring in 11 (6.3%) patients. A mild increase in serum AST levels occurred in patients started on statin therapy when compared

**TABLE 3. Association Between Clinical Characteristics and New-Onset Dyslipidemia Following LT**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Unadjusted</th>
<th>Adjusted*</th>
<th>Adjusted†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR 95% CI</td>
<td><em>P</em> Value</td>
<td>HR 95% CI</td>
</tr>
<tr>
<td>Age</td>
<td>1.02 0.99-1.03 0.07</td>
<td>1.00 0.99-1.03 0.83</td>
<td>— — —</td>
</tr>
<tr>
<td>Sex, male</td>
<td>0.66 0.48-0.92 0.01</td>
<td>0.67 0.44-1.02 0.06</td>
<td>0.68 0.46-1.01 0.06</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Caucasin 1.00 — — 1.00 — —</td>
<td>— — —</td>
<td>— — —</td>
</tr>
<tr>
<td></td>
<td>African American 0.89 0.61-1.31 0.56</td>
<td>0.99 0.61-1.62 0.98</td>
<td>— — —</td>
</tr>
<tr>
<td>Etiology</td>
<td>Alcohol 1.00 — — — 1.00 — —</td>
<td>1.00 — —</td>
<td>1.00 0.36-0.83 0.004</td>
</tr>
<tr>
<td></td>
<td>HCV 0.53 0.35-0.81 0.003</td>
<td>0.56 0.36-0.88 0.01</td>
<td>0.54 0.36-0.83 0.004</td>
</tr>
<tr>
<td></td>
<td>NASH 1.63 0.98-2.71 0.06</td>
<td>1.37 0.78-2.39 0.27</td>
<td>1.48 0.88-2.47 0.14</td>
</tr>
<tr>
<td></td>
<td>Obesity 1.11 0.75-1.62 0.61</td>
<td>0.94 0.60-1.46 0.78</td>
<td>— — —</td>
</tr>
<tr>
<td></td>
<td>Hypertension 1.51 1.10-2.07 0.01</td>
<td>1.14 0.77-1.70 0.51</td>
<td>— — —</td>
</tr>
<tr>
<td></td>
<td>Diabetes 1.46 1.05-2.02 0.01</td>
<td>1.14 0.76-1.70 0.53</td>
<td>— — —</td>
</tr>
<tr>
<td></td>
<td>CAD 1.80 1.29-2.53 &lt;0.001</td>
<td>1.54 1.03-2.31 0.04</td>
<td>1.56 1.08-2.27 0.02</td>
</tr>
</tbody>
</table>

*The following variables were included in the model: age, sex, ethnicity, etiology, obesity, hypertension, diabetes, and CAD before LT.
†The following variables were included in the model: sex, etiology, and CAD.
MORTALITY

Over the study duration, 120 (24.2%) patients died with a median time to death from LT of 2.1 years (IQR, 0.5-4.6 years). The 3 major causes of post-LT deaths included malignancy (23.3%, n = 28), CVD (19.2%, n = 23), and infections (17.5%, n = 21). After adjusting for age, sex, ethnicity, primary etiology of liver disease, obesity, hypertension, and diabetes at LT, no statistically significant association was observed between mortality and presence of CAD (HR, 0.91; 95% CI, 0.54-1.55) or severity of CAD (HR, 1.11; 95% CI, 0.52-2.36; Fig. 4A). Statin therapy had a protective effect on survival, and it was associated with reduced mortality (HR, 0.25; 95% CI, 0.12-0.49; P < 0.001). The beneficial effects of statins on survival persisted even after adjusting for age, sex, ethnicity, etiology of liver disease, obesity, hypertension, diabetes, and CAD presence at LT (Fig. 4B). The association between mortality and statin use was further assessed by evaluating the interaction between CAD and statin use, which was not found to be significant (HR, 0.27; 95% CI, 0.06-1.17).

Aspirin use (regardless of statin use) did not impact overall survival in unadjusted analysis (HR, 0.82; 95% CI, 0.51-1.34) or after adjusting for age, sex, ethnicity, etiology of liver disease, obesity, hypertension, diabetes, and CAD presence at LT (adjusted HR, 0.69; 95% CI, 0.38-1.25). In patients on statins, aspirin use was associated with no survival benefit (HR, 0.31; 95% CI, 0.06-1.55). Finally, no evidence of an interaction between aspirin and CAD on overall survival (HR, 1.73; 95% CI, 0.52-5.75) was noted after adjusting for age, sex, ethnicity, etiology of liver disease, obesity, hypertension, and diabetes.

Discussion

A major milestone after LT is 1-year survival, which has steadily increased over the past few decades; however, longterm survival remains significantly lower when compared with age- and sex-matched controls in the non-LT population. Efforts to improve longterm mortality require a granular understanding of key contributors to post-LT mortality, particularly CVD,
which is one of the leading contributors to long-term mortality following LT.\(^{1,5}\) In the present study, we confirmed the importance of CVD-associated mortality following LT but also noted that the presence and severity of CAD at the time of LT did not impact overall or cardiovascular-related mortality. Because all potential LT candidates with obstructive CAD undergo revascularization prior to LT, the natural history of CAD in LT is therefore altered.

It is possible that the current study was not adequately powered to detect the smaller effect size because the number of patients with revascularized CAD was relatively small. Biologically, the risk of poor outcomes following coronary thrombosis is linked to the robustness of collateral circulation.\(^{26}\) Therefore, slowly developing coronary stenosis with an adequate collateral flow is less likely to lead to fatal events or sequelae following a coronary event. In contrast, rapidly developing stenosis due to accelerated atherosclerosis, as has been demonstrated following LT with presumably inadequate collateral formation, is more likely to lead to fatal outcomes or lasting sequelae.\(^{27}\) Prior studies in LTRs have demonstrated a close association between LT, atherogenic lipoproteins, and proinflammatory mediators.\(^{9,10}\) Furthermore, a longitudinal increase in markers of endothelial dysfunction following LT has also been reported.\(^{28}\) These factors are linked to atherosclerosis and give credence to the theory that rapid atherosclerosis following LT likely plays a more important role in post-LT outcomes than the presence of native CAD present at the time of LT.\(^{9,10}\)

Dyslipidemia is a strong, independent, and, more importantly, modifiable risk factor for CAD and CVD-associated mortality.\(^{29,30}\) In the present study, we defined a time-dependent increase in the prevalence of dyslipidemia in LTR that varied with the etiology of end-stage liver disease requiring LT. These findings reaffirmed prior published reports demonstrating that the greatest prevalence of dyslipidemia was among patients transplanted for NASH cirrhosis.\(^{1}\) Dyslipidemia in patients after LT was largely characterized by a uniform increase in serum triglycerides, total cholesterol, and a concurrent decrease in HDL-C. Factors associated with the development of dyslipidemia included diabetes and NASH as the etiology of chronic liver disease, suggesting that these should potentially be targeted to reduce future risk. Mechanistic studies have previously demonstrated that cyclosporine leads to dyslipidemia by reducing the activity of hepatic cholesterol-7α-hydroxylase, a rate-limiting enzyme in bile acid synthesis, and thereby by reducing the incorporation of cholesterol into bile acids.\(^{31}\) Furthermore, cyclosporine also increases hepatic lipoprotein production and reduces lipoprotein clearance.\(^{32}\) Recent studies also implicated the association between cyclosporine and more atherogenic lipoprotein subparticles, such as small-dense LDL-C, very low-density particle size, and concentration.\(^{9,10}\) Thus, it may be prudent to use tacrolimus as the main immunosuppressant in LTRs at risk for developing dyslipidemia, such as patients who are obese, diabetic, or transplanted for NASH cirrhosis, to mitigate the effects of immunosuppression on dyslipidemia following LT.

Dyslipidemia is a major modifiable risk factor for CAD, and the mainstay of therapy includes at least the use of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors or statins.\(^{22}\) There is currently an abundance of literature demonstrating the efficacy of statins in primary and secondary prophylaxis for reducing myocardial infarction, stroke, and CVD-associated mortality.\(^{29,33,34}\) Furthermore, statin therapy has demonstrated a mortality benefit even in patients with chronic liver disease\(^{35}\); however, statins are often avoided in patients with chronic liver disease for fear of hepatotoxicity, even in patients with obstructive and severe CAD.\(^{16,36}\) In a recent study of patients with decompensated cirrhosis, statins were safely tolerated and did not impact survival or the need for transplantation.\(^{16}\) Our study expands the published literature by demonstrating that statin therapy is safe after LT and is not associated with hepatotoxicity. Furthermore, statins are underused in LTRs for whom there is an indication either due to dyslipidemia or presence of known CAD.

This underuse is concerning because the use of statin therapy after LT was associated with a reduction in overall mortality. Although adverse effects can limit the use of statin therapy, in our study cohort, only a small number of patients developed any reportable adverse effects. Thus, statin therapy is safe and effective with limited adverse effects after LT, and it should be aggressively initiated and titrated to improve long-term survival following LT. Even though the results from the current study trend to a positive effect of aspirin use on survival, the CI is wide and does not allow us to give any definite conclusion. Future studies with larger sample sizes will be needed to explore this complex interaction. Males and patients with HCV-related liver disease were less likely to be on statins, whereas patients with
hypertension were more likely to be on aspirin ther-
apy. This could be from multiple interrelated factors,
including awareness, social status, and income level as
well as other coexisting medical problems.

There are several limitations worth mentioning
in the current study. First, because all patients with
obstructive CAD were revascularized, the current
study is not able to provide the true natural history
of obstructive CAD following LT; however, the study
population is representative of patients receiving LT
because those with obstructive CAD not amenable to
revascularization were excluded from further LT con-
sideration. Second, although the total sample size was
large in the present study, the number of deaths attrib-
utable solely to CVD was relatively small to determine
a key relationship between pre- and post-LT clinical
parameters and CVD-associated mortality. The survival benefit from aspirin use may not have been demonstrated due to a type II error. This limitation will be a major limitation of any single-center study and requires a well-designed prospective natural
history with a large sample size to address it.

Finally, because of the retrospective design of the
current study, we are unable to explore what physi-
cian- and patient–related factors may have influenced
the decision not to initiate statins. Understanding this
decision-making process is of paramount importance
if we are to improve the management of CVD follow-
ning LT. Prior survey-based studies have demonstrated
that only a small minority of primary care physicians
feel comfortable taking care of LTRs, and the deci-
sion to not start statins in LTRs, therefore, may be
reflective of this. However, well-planned studies that
use mixed-methods approaches are necessary to truly
understand the underutilization of statins in LTRs.

In summary, CAD at the time of LT does not impact
overall survival following LT, suggesting the role of
accelerated atherosclerosis after LT. Statin therapy is
safe, well tolerated, and confers a mortality benefit in
LTRs, but it is underused.

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