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The Relationship between Coronary Artery Disease and Cardiovascular Events Early After Liver Transplantation

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Abstract

Cardiovascular complications are major contributors to mortality at liver transplantation(LT). However, the impact of coronary artery disease(CAD) on these complications is not well-understood as the literature is limited by non-invasive assessment of CAD, which is suboptimal in patients with cirrhosis. Thus, the current study evaluated cardiovascular events at LT stratified according to presence and severity of CAD quantified on coronary angiography.

Methods—All patients who had LT from January 2010 to January 2017 were evaluated(N=348) but analysis was restricted to patients who had coronary angiography prior to LT(N=283). Protocol coronary angiography was performed in all patients ages >50 years, history of CAD, abnormal cardiac stress test or risk factors for CAD. The primary outcome was a cardiovascular composite outcome including myocardial infarction(MI), cardiac arrest, stroke, cardiac death, heart failure or arrhythmia occurring within 4 weeks after LT.

Results—CAD was present in 92(32.5%) patients and 32(11.3%) had obstructive CAD. During the study period 72(25.4%) patients met the primary cardiovascular outcome, the most common being arrhythmia(N=59 or 20.8%). Non-ST elevation MI occurred in 11(3.9%) of patients. A total

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of 10 deaths(3.5%) occurred, of which 6(2.1%) were attributable to cardiac death. There was no evidence of a relationship between presence and severity of CAD and composite cardiovascular events. In multiple regression modeling, only diabetes[OR 2.62, 95%CI(1.49, 4.64), P<0.001] was associated with the likelihood of having a cardiovascular event.

Conclusion—Cardiovascular disease mortality is the most important contributor of early mortality after LT but is not related to the severity of CAD.

Keywords

Coronary artery disease; cirrhosis; cardiovascular events; Liver transplantation

INTRODUCTION

Cardiovascular disease (CVD) is an important contributor to morbidity and mortality during and immediately after liver transplantation (LT).(1,2) More importantly, the presence and severity of coronary artery disease (CAD) has been linked to worse outcomes at LT.(2) The gold standard for CAD assessment is coronary angiography but it is often deferred in many patients with decompensated cirrhosis due to perceived higher risk of complications, thereby introducing a selection bias in the published literature.(3–5) This is compounded further by the suboptimal diagnostic performance of non-invasive cardiac testing in patients with cirrhosis due to blunted heart rate response, body habitus, edema, deconditioning and impaired functional status.(6–8) Thus, it is difficult to interpret the findings of the published literature that have evaluated the impact of underlying CAD on CVD events at the time of LT that used non-invasive cardiac assessment.(9,10) Using coronary angiography, a recent study demonstrated higher prevalence of CAD in potential LT waitlist registrants compared to the general population (11,12), however, due to relatively small sample size the association between CAD and CVD events could not be thoroughly interrogated. The study does highlight the fact that CAD is more common among potential LT candidates and its impact should therefore be clearly defined.(11)

The spectrum of liver disease and cause of cirrhosis is rapidly evolving (13) and while cirrhosis related to nonalcoholic steatohepatitis (NASH) was relatively uncommon during the 1990s and early 2000s, NASH is now the fast growing indication for LT among new LT waitlist registrants (14). NASH is closely associated with the metabolic syndrome and CAD (15) and in patients with decompensated cirrhosis due to NASH, the presence and severity of CAD was much higher compared to other etiologies of cirrhosis(11). The published literature linking CAD to CVD events largely included patients with viral hepatitis with small contribution from patients with NASH cirrhosis.(1,2) Thus, given these limitations in the published literature, we conducted the following study in patients with decompensated cirrhosis with protocol coronary angiography prior to LT to (1) granularly define the incidence of CVD events (2) link CVD events to CAD and (3) identify predictors of CVD events at LT.

METHODS

All new LT waitlist registrants are enrolled in to a natural history study at the authors' institution and the data is collected prospectively at Virginia Commonwealth University Medical Center. The Virginia Commonwealth University Institutional Review Board reviewed and approved the current study. The analysis of the data did not require consent. The manuscript was reviewed and approved by all authors prior to submission.

Patient Population

The study cohort consisted of adult patients (ages 18 or older) with decompensated cirrhosis who received a LT from January 1, 2010 to January 1, 2017. Per institutional policy, coronary angiography was performed in all patients over the age of 50 years as part of the CAD assessment. In patients who were younger than 50 years, coronary angiography was reserved for patients with (1) prior history of CAD, (2) risk factors for CAD (diabetes, hypertension, obesity, family history of CVD, smoking history) or (3) abnormal or non-diagnostic non-invasive cardiac stress testing. Patients who did not have coronary angiography performed as a part of LT evaluation were excluded. Additional exclusion criteria included combined liver-heart transplant, re-transplantation, or history of another solid organ transplant. Demographic, laboratory, radiological, clinical, and surgical information was retrieved from institutional maintained database of LT recipients.

Coronary Angiography

All patients underwent elective coronary angiography and the presence of CAD was defined as any degree of stenosis in any of the coronary arteries as determined by visual inspection on coronary angiography(16). The CAD was further stratified as non-obstructive (stenosis <50%) and obstructive (stenosis ≥ 50) (17). Percutaneous coronary intervention (PCI) was performed in patients with obstructive CAD in multidisciplinary committee consisting of cardiology, anesthesiology, hepatology and transplant surgery. The decision to pursue PCI was individualized to patients taking into account the severity of the obstruction, number of vessels involved, the location of the obstruction (e.g. proximal vs. distal), collateral circulation and the functional severity of the lesion. All patients requiring PCI underwent stenting with bare metal stent and were subsequently managed on dual anti-platelet therapy with aspirin and clopidogrel for 4 weeks per protocol. After 4 weeks, patients were transitioned to and maintained on aspirin monotherapy. The intra-operative care of these patients was standardized to minimize CVD associated outcomes and is presented in detail in supplementary material.

Clinical Outcome

The primary outcome was a composite cardiovascular endpoint consisting of any of the following: myocardial infarction (MI), heart failure, cardiac arrest, stroke, cardiac death or arrhythmia requiring treatment within 4 weeks of LT. The diagnosis of MI was based on an increase in serum levels of troponin I, which may be accompanied by electrocardiogram (ECG) findings of sub endocardial or transmural MI.(18) This was stratified further based on ECG findings of elevation of ST-segment (ST-elevation acute coronary syndrome) or in the absence of ST-elevation (Non- ST-elevation acute coronary syndrome). (18) The diagnosis

of heart failure was based on signs and symptoms of fluid overload along with evidence of ventricular dysfunction.(19) Patients with reduced ejection fraction (<40%) or those with severe diastolic dysfunction as noted on echocardiography were excluded from LT consideration and therefore, not included in the current study. Arrhythmia included supraventricular arrhythmias, ventricular arrhythmias and conduction delay arrhythmias. (20) Arrhythmias were defined according to the definitions endorsed by American Heart Association as published previously.(21,22) The individual definitions of these arrhythmias is provided in supplementary material. Cardiac arrest was defined as absence of palpable pulse and recordable blood pressure in an unresponsive patient with subsequent resuscitation.(23) Stroke was defined as a neurological deficit attributed to an acute focal injury of the central nervous system lasting 24 hours or until death.(24) Cardiac death was defined as death in the setting of MI, ventricular arrhythmias, cardiogenic shock, or if the death was sudden and unexplained.(23) Secondary endpoints included individual CVD events outlined above. All events were independently verified by the authors by careful review of the electronic medical record and source documents. All events were independently verified by four reviewers. In cases of disagreements, events were discussed in committee until a consensus was reached.

Statistical Analysis:

The descriptive statistics are reported as means and standard deviations (SD) for continuous variables, and frequencies and percentages for categorical variables. Bivariate analyses between the presence of CAD and clinical characteristics were performed via Pearson chi-squared test or Fisher's exact test for categorical variables and T-test for continuous variables. In the initial analysis, presence and severity of CAD was quantified and linked to presence of clinical and laboratory parameters.

We evaluated the incidence of CVD events within 4 weeks of LT. The bivariate associations between demographic and clinical characteristics and incidence of CVD were assessed using T-test for continuous variables and Pearson chi-square test or Fisher's exact test for categorical variables. To evaluate the relationship between clinical and biochemical parameters and CVD events, a multiple logistic regression model was built to obtain adjusted odds ratios (OR) for CVD. These covariates included bio-clinical data (age, gender, body mass index, etiology of liver disease, diabetes, dyslipidemia, hepatitis C], the presence of CAD, requirement for PCI(25,26) and intra-operative parameters (blood transfusion, intra-operative hypotension, total operative time). A minimum Akaike information criteria value was used to determine which variables were included in the stepwise model. Statistical analyses were conducted in R (Version 3.4.2, R Foundation for Statistical Computing, Vienna, Austria), with a significance level of 0.05.

RESULTS

Patient Characteristics:

A total of 358 patients underwent LT from January 1, 2010 to January 1, 2017, and of those, 283 (79.1%) patients had protocolled coronary angiography as part of their LT evaluation. The baseline characteristics of the study cohorts are summarized in Table 1. The majority of

the cohort that had coronary angiography were males and non-Hispanic Caucasian. The mean age of the cohort was 57.9 ± 6.3 years and the mean MELD-sodium at LT was 23 ± 8.1 . Hepatitis C virus (HCV) related cirrhosis was the most common etiology of chronic liver disease (49.5%), followed by NASH (18.4%) and alcoholic cirrhosis (17.3%).

CAD risk factors

In the study cohort, the distribution of hypertension, diabetes and obese was common and varied by the etiology of cirrhosis (Table 1). Obesity was far more common in the patients with NASH cirrhosis as compared to patients with HCV or alcoholic cirrhosis (71.2% vs. 31.4% vs. 32.7%, $p < 0.001$). Similarly, diabetes and dyslipidemia were more common in patients with NASH compared to other etiologies of cirrhosis (Table 1). In contrast, smoking was more common in patients with HCV (77.1%) and alcohol (67.3%) related cirrhosis compared to NASH cirrhosis (46.2%) ($P < 0.001$). The serum low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides and total cholesterol levels were similar in patients with and without CAD and were similar across etiology of cirrhosis (Table 1 & Supplemental 1). Finally, serum lipid profile was similar across severity of CAD, while a tendency of a lower prevalence of obesity was noted among those with obstructive CAD (Supplemental Table 2).

Coronary Artery Disease

CAD was present in 92 (32.5%) patients with 32 (11.3% of the cohort) had obstructive CAD (Supplemental Table 1). Patients with CAD were more likely to be older (59 ± 6 years vs. 57 ± 6 , $P = 0.04$). CAD was more common in patients with NASH cirrhosis compared to HCV and alcoholic cirrhosis (Table 1). Similarly, obstructive CAD was more common among patients with NASH cirrhosis compared to HCV and alcoholic cirrhosis (Figure 1). Compared to patients with no CAD, the prevalence of diabetes was higher in patients with obstructive CAD (Supplemental table 2). Of the 32 patients with obstructive disease, 20 patients (64%) had percutaneous coronary intervention (PCI) performed.

Cardiovascular Disease Outcomes

A total of 72 (25.4%) patients had the composite cardiovascular outcomes during the study period after LT (Table 2). The primary outcome was not associated with presence of CAD or presence of obstructive CAD (Table 2), however, a trend in severity of CAD and primary outcome was noted (Figure 2A). In patients with CAD, severity of obstructive disease ($<50\%$ vs. $50-70\%$ vs. $>70\%$ lesion), and vessels involved (single vs. multi-vessel disease) did not show evidence of being associated with primary outcome. (Supplementary material) Of the ECG findings, presence of atrial fibrillation prior to LT was strongly associated with primary outcomes. The most common cardiovascular event was cardiac arrhythmia, occurring in 59 patients (20.5%) (Figure 2B). The most common cardiac arrhythmia was atrial fibrillation ($N=28$), followed by symptomatic bradycardia ($N=12$), supraventricular tachycardia ($N=10$). Ten arrhythmias were associated with hemodynamic instability and the most common of these include asystole ($N=4$), bradycardia ($N=3$), and atrial fibrillation ($N=2$) (Supplementary material).

The relationship between obstructive CAD and likelihood of meeting primary CVD outcome approached statistical significance ($P=0.19$; Table 2) and was largely attributed to a non-significant increase in arrhythmias (Table 2). Eleven patients (3.9%) had non-ST elevation MI, while no patients had ST-elevation MI and interestingly, only 3 occurred in patients with documented CAD. A total of 10 death (3.5%) occurred within 4 weeks of LT and 6 (2.1%) were attributable to CVD, however, only 2 cardiac death occurred in patients with CAD (Figure 2B). Finally, no association between need for PCI and CVD related outcomes after LT was noted (Table 2). Patients with a CVD related outcome had higher prevalence of diabetes mellitus (48.6% vs. 28.4%, $P=0.003$) (Table 3) but no differences in other bio-clinical parameters including age, gender, smoking history, hypertension, dyslipidemia, and family history were observed.

Predictors of Cardiovascular Disease Outcomes

In simple logistic regression analysis, diabetes (OR 2.38, 95% Confidence Interval [CI] 1.37-4.14, $P=0.002$), was associated with having a cardiovascular outcome after LT. After adjusting for other covariates in multiple logistic regression, only diabetes (OR=2.62; $P<0.001$) was found to be associated with likelihood of having a cardiovascular event within 4 weeks after LT adjusting for age and presence of hepatitis C (Table 4). Finally, intra-operative red blood cell transfusion was associated with primary outcomes (OR 1.08, 95% CI 1.02, 1.13; $P=0.01$).

DISCUSSION:

Liver transplantation is a complex surgery that puts immense stress on the cardiovascular system and accurate diagnosis of CAD prior to LT is important to identify patients with acceptable medical risk for LT and to optimize CAD management prior to LT (9,27,28). There is limited data with regards to impact of CAD on early cardiovascular outcomes following LT using coronary angiography as the reference test.(1,27,29) In the present study, the overall risk of a composite cardiovascular outcome within 4 weeks after LT was nearly 30% with cardiac arrhythmias being the most common complication. No significant association was noted between CAD and the likelihood of having an early cardiovascular event, contrary to published literature that shows severity of CAD was linked to fatal cardiovascular events.(2,9,27) This discrepancy in our findings and published literature likely results from a number of factors. First, most patients with CAD either had non-obstructive or re-vascularized obstructive CAD, which likely reduced the inherent risk of cardiovascular events associated with native CAD.(29) Second, the likelihood of a cardiovascular event at or immediately after LT results from tremendous physiological stress of LT rather than ischemia, which is supported in our cohort demonstrating no association between CAD and peri-LT MI or cardiac death. Third, patients with NASH are at greatest the risk of cardiovascular events (30,31), which was under represented in our cohort and therefore, the impact of NASH on peri-LT cardiac outcomes may be due to type II error. Finally, patients at greatest risk for intra-operative complications from extensive CAD are excluded from LT consideration thus, the current study represents a biased cohort that was deemed to be low risk for potential complications at LT. This is in contrast to prior studies linking CAD to cardiovascular outcomes after LT, where protocol coronary angiography was

not uniformly performed.(32,33) Although presence of CAD alone was not significantly associated with risk of arrhythmia, a trend between obstructive CAD and arrhythmia was noted despite coronary revascularization. This likely results from altered myocardium that is more susceptible to blood loss, ischemia, anesthetics and electrolyte abnormalities thus resulting in arrhythmias in patients with obstructive CAD in spite of revascularization (34,35).

A key negative finding of the current study is the low incidence of MI or heart failure and did not contribute to cardiac mortality. The MI observed during the study period were non-ST-elevation MI and likely resulting from demand ischemia from surgical stress. Similarly, heart failure likely became clinically evident in patients with borderline heart failure and depressed ejection fraction that was masked by hyperdynamic circulation commonly seen in decompensated cirrhosis.(36,37) While the observed CVD related mortality in the study cohort is similar to prior published literature, it was not negligible.(32) This is an important concept as this occurred despite identification and pre- and peri-operative patient optimization and may represent a fixed cardiac mortality that results from stress of LT surgery and may not be entirely avoidable as LT itself not a predictable procedure. To better understand the key drivers of this peri-operative CVD mortality, large multicenter cohorts with patient-level data are required.

There was a trend towards lower prevalence of obesity in patients with obstructive CAD. As patients progress to cirrhosis, the weight loss and sarcopenia is common,(38) thus, the CAD noted at LT evaluation is not truly reflective of the co-morbidities that lead to its development. Additionally, weight itself is an imperfect predictor of CVD, as it fails to account for distribution of adiposity, which is a better predictor of CVD. (39). Aside from obesity, other cardiometabolic risk factors such as diabetes, hypertension or dyslipidemia may have predisposed to development of CAD. Similar to obesity, no association between hypertension and obstructive CAD was observed and may also be due to the fact that hypertension improves due to systemic vasodilatation observed in patients as they progress to cirrhosis.(40) Similarly, due to synthetic hepatic failure, dyslipidemia may also improve as patients progress to cirrhosis. Since the sample size of patients with obstructive CAD is relatively small, it is important not to over-interpret these associations as they may be subject to type II error. Prior studies have shown an association between CVD outcomes and obesity and hypertension (9,10), however, the follow up in these studies was 12 months after LT, while we limited our follow to 4 weeks following LT. Thus, the factors that drive CVD events are variable as the events occurring within 4 weeks are more likely to be related to the physiological stresses of LT itself, whereas, events occurring closer to 12 months are less likely related to LT itself. Finally, none of the studies had protocol coronary angiography and given the sub-optimal performance of non-invasive CAD assessment in patients with cirrhosis, it is difficult to ascertain whether the cardiovascular outcome may have resulted from undiagnosed CAD.(9,32)

The large sample size with protocol driven coronary angiography are key strengths of the current study that fill a major gap in knowledge within the field of LT. Additionally, linking the presence and severity of CAD to cardiovascular events allows for a more robust and granular assessment of key contributors of cardiovascular events at the time of LT. It is

imperative that the conclusions of the current study are evaluated in the context of its limitations. First, all potential LT recipients deemed to be at high CVD risk are either excluded or re-vascularized, thus leading to selection bias as the relationship between native CAD and cardiovascular events cannot be fully explored. However, most patients with severe CAD that is not amenable to re-vascularization are excluded from LT consideration across transplant centers, thus, the cohort studied is representative of patients receiving LT. Due to smaller sample size of patients with NASH cirrhosis, we are unable to fully evaluate the interplay between NASH, CAD and cardiovascular outcomes at the time of LT. However, the current limitation should be examined in the context of published literature that shows that the proportion of patients with NASH receiving a LT has increased from 0.1% or less in 1995–2000 to 3.5% in 2005 and 17.4% in 2014.(41,42) The prevalence of NASH in the study population is consistent with published literature and is once again representative of patients receiving LT. Thus, to evaluate the relationship between NASH, CAD and CVD events, a larger multicenter cohort is required to address this issue.

In conclusion, cardiac arrhythmias are the most common cardiovascular complication after LT but are not associated with presence or severity of CAD after pre-LT cardiac optimization. CVD related mortality is the major cause of mortality early after LT and underscores the importance of accurate cardiovascular risk assessment in potential LT waitlist registrants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CVD	Cardiovascular disease
LT	Liver transplantation
CAD	Coronary artery disease
NASH	Nonalcoholic steatohepatitis
PCI	Percutaneous coronary intervention
MI	Myocardial infarction
ECG	Electrocardiogram
SD	Standard deviations
OR	Odds ratio

HCV Hepatitis C virus

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SUMMARY

The key novel findings and its implication in the current manuscript are summarized below:

1. Cardiac arrhythmias are the most common cardiovascular event after liver transplantation
2. The risk of cardiovascular events during the immediate post-transplant period is not associated with presence or severity of coronary artery disease.
3. Overall mortality immediately after liver transplantation is high, cardiovascular mortality is the greatest contributor to this.

Figure 1:
Prevalence of coronary artery disease by etiology of chronic liver disease

Figure 2A:

Cardiac events at time of liver transplantation stratified according to severity of coronary artery disease

Figure 2B:
Individual cardiac events stratified according to severity of coronary artery disease

Table 1.

Distribution of clinical characteristics and laboratory test by liver disease

Characteristics	Liver disease				p-value ^a
	Entire cohort N=283	ETOH N=49	Hepatitis C N=140	NASH N=52	
Obesity	109 (38.5%)	16 (32.7%)	44 (31.4%)	37 (71.2%)	<0.001 ^b
Smoking					<0.001 ^b
Never	102 (36%)	16 (32.7%)	32 (22.9%)	28 (53.8%)	
Prior or Current	181 (64%)	33 (67.3%)	108 (77.1%)	24 (46.2%)	
Hypertension	148 (52.3%)	27 (55.1%)	70 (50%)	35 (67.3%)	0.10 ^b
SBP, mmHg	119.7 ± 19.0	119.6 ± 17.6	121.1 ± 20.5	116.8 ± 17.6	0.46
DBP, mmHg	68.4 ± (11.2)	66.2 ± 10.2	70.2 ± 11.6	66.1 ± 11.8	0.90
History of CAD	114 (40.3%)	16 (32.7%)	60 (42.9%)	27 (51.9%)	0.15 ^b
MI	4 (1.4%)	2 (4.1%)	1 (0.7%)	1 (1.9%)	0.13
Dyslipidemia	76 (26.9%)	16 (32.7%)	22 (15.7%)	24 (46.2%)	<0.001 ^b
FHx CAD	90 (31.8%)	20 (40.8%)	37 (26.4%)	17 (32.7%)	0.16 ^b
Metabolic/Renal					
Diabetes mellitus	95 (33.6%)	13 (26.5%)	38 (27.1%)	34 (65.4%)	<0.001 ^b
Dialysis	26 (9.2%)	3 (6.1%)	12 (8.6%)	6 (11.5%)	0.63
Total cholesterol, mg/dL ^c	137.5 ± 68.5	127.9 ± 52.2	115.4 ± 49.3	142.3 ± 71.7	0.23
HDL, mg/dL ^c	36.9 ± 15.6	35.6 ± 14.1	33.9 ± 14.8	38.6 ± 16.3	0.44
LDL, mg/dL ^c	97.1 ± 42	0 ± 0	63 ± 36.4	95 ± 11.3	0.19
Triglycerides, mg/dL ^c	85.9 ± 59.3	76.8 ± 32.2	70 ± 22.4	91.2 ± 43.7	0.24

^aT-test for continuous variables and Fisher's exact test for categorical variables.^bChi-square test.^cMissing data on >50% patients

CAD, Coronary artery disease; DBP, Diastolic blood pressure; HDL, high-density lipoproteins; LDL, low-density lipoproteins; SBP, Systolic blood pressure;

Table 2.

Distribution of cardiovascular disease outcomes by CAD diagnosis

OUTCOMES	Entire Cohort	CAD			Obstructive CAD			Revascularization prior to LT		
		No	Yes	p-value ^a	No	Yes	p-value ^a	No	Yes	p-value ^a
N	283	191	92		60	32		73	19	
Primary Outcome	72 (25.4%)	44 (23.0%)	28(30.4%)	0.23 ^b	15 (25.0%)	13(40.6%)	0.19 ^b	19 (26.0%)	9 (47.4%)	0.13 ^b
Secondary Outcomes										
Myocardial Infarction	11 (3.9%)	8 (4.2%)	3 (3.3%)	>0.99	3 (5.0%)	0 (0.0%)	0.55	2 (2.7%)	1 (5.3%)	0.51
Arrhythmia	59 (20.8%)	35 (18.3%)	24 (26.1%)	0.18 ^b	12 (20.0%)	12(37.5%)	0.08 ^b	17 (23.3%)	7 (36.8%)	0.25 ^b
Heart failure	5 (1.8%)	4 (2.1%)	1 (1.1%)	>0.99	0 (0.0%)	1 (3.1%)	0.35	0 (0.0%)	1 (5.3%)	0.21
Cardiac Death	6 (2.1%)	4 (2.1%)	2 (2.2%)	>0.99	2 (3.3%)	0 (0.0%)	0.54	2 (2.7%)	0 (0.0%)	>0.99
Stroke	2 (0.7%)	1 (0.5%)	1 (1.1%)	0.55	0 (0.0%)	1 (3.1%)	0.35	0 (0.0%)	1 (5.3%)	0.21

^aFisher's exact test.^bPearson chi-squared test

CAD, Coronary artery disease; LT, Liver transplantation;

Table 3.

Distribution of clinical characteristics based cardiovascular disease outcomes

Characteristics	Cardiovascular disease outcomes		
	No N=211	Yes N=72	p-value ^a
Age, years	57.6 ± 6.2	58.9 ± 6.7	0.15
Male	155 (73.5%)	55 (76.4%)	0.74
Race			0.83
Caucasian	152 (76.4%)	55 (78.6%)	
African American	47 (23.6%)	15 (21.4%)	
BMI, kg/m ²	29.3 ± 6.0	28.8 ± 4.9	0.49
Obesity	83 (39.3%)	26 (36.1%)	0.73
Smoking			0.67
Never	78 (37.0%)	24 (33.3%)	
Prior or Current	133 (63.0%)	48 (66.7%)	
History of cardiac disease			
Hypertension	111 (52.6%)	37 (51.4%)	0.97
History of CAD	80 (37.9%)	34 (47.2%)	0.21
Dyslipidemia	52 (24.6%)	24 (33.3%)	0.20
Family history of CAD	71 (33.6%)	19 (26.4%)	0.32
Metabolic/Renal			
Diabetes mellitus	60 (28.4%)	35 (48.6%)	0.003
Dialysis	18 (8.5%)	8 (11.1%)	0.68
Etiology of liver disease			
Alcohol	40 (22.3%)	9 (14.5%)	
Hepatitis C	101 (56.4%)	39 (62.9%)	
NASH	38 (21.2%)	13 (22.6%)	
MELD	20.4 ± 8.2	20.4 ± 6.8	0.99
MELD-Sodium	23 ± 8.3	23 ± 7.4	0.96

^aT-test for continuous variables and Chi-square test for categorical variables.

BMI, Body mass index; CAD, Coronary artery disease; CLD, Chronic liver disease MELD, Model for End-Stage Liver Disease; NASH, Nonalcoholic steatohepatitis;

Table 4.

Association between clinical characteristics and cardiovascular disease outcomes

Variable	Comparison	Unadjusted OR N=283			Adjusted OR N=283			Adjusted OR N=283		
		OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value
Age	1-year increase	1.04	(0.99, 1.09)	0.13	1.03	(0.99, 1.09)	0.15	1.04	(0.99, 1.09)	0.10
CAD	CAD vs. non-CAD	1.46	(0.83, 2.54)	0.18	1.20	(0.67, 2.14)	0.53			
Dyslipidemia	Dyslipidemia vs. No dyslipidemia	1.53	(0.85, 2.72)	0.15	1.45	(0.77, 2.72)	0.25			
Diabetes mellitus	DM vs. non-DM	2.38	(1.37, 4.14)	0.002	2.48	(1.39, 4.42)	0.002	2.62	(1.49, 4.64)	<0.001
Hepatitis C	Hepatitis C vs. non-hepatitis C	1.29	(0.75, 2.21)	0.36	1.59	(0.89, 2.89)	0.12	1.47	(0.84, 2.59)	0.18

CAD, Coronary artery disease; CI, confidence interval; DM, Diabetes mellitus; OR, Odds ratio;