Title
The Association Between Left Atrial Volume Index and Liver Transplant Survival

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Publication Date
2016

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

The Association Between Left Atrial Volume Index and Liver Transplant Survival

A thesis submitted in partial satisfaction

of the requirements for the degree Master of Science

in Clinical Research

by

Brent David Ershoff

2016

ABSTRACT OF THE THESIS

The Association Between Left Atrial Volume Index

and Liver Transplant Survival

By

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Masters of Science in Clinical Research

University of California, Los Angeles, 2016

Professor Robert M. Elashoff, Chair

Background: Cardiac complications are the leading cause of long-term non-graft related mortality following liver transplantation. While the Scientific Registry of Transplant Recipients (SRTR) reports multiple risk factors for post-operative mortality, there are currently no cardiac specific risk factors included in the survival models. Cirrhotic cardiomyopathy, a spectrum of cardiovascular changes associated with end stage liver disease including diastolic dysfunction (DD), is well described. Left atrial volume index (LAVI) is an echocardiographic measure of DD, and has been associated with mortality in many populations. Unlike transmitral inflow

velocities which are load dependent, LAVI is considered to be a more sensitive and stable measurement of DD. To date, there is limited data evaluating the effect of LAVI on mortality following liver transplantation. The aims of this study were to determine whether LAVI is an independent predictor of post-liver transplant mortality, and whether LAVI improves the ability to predict mortality beyond known risk factors.

Methods: We performed a retrospective cohort study of patients ≥ 18 years of age who underwent liver transplantation between July 2011 and June 2014 at the University of California, Los Angeles, and who had their preoperative transthoracic echocardiograms performed at our center. The primary outcome was time to mortality, and the primary predictor was LAVI, dichotomized at 28ml/m^2. Known risk factors of post liver transplant mortality identified from the SRTR database were collected as covariates. A multivariable Cox regression model was built using a backwards stepwise selection procedure to assess the effect of LAVI on post-operative mortality.

Results: Of the 254 patients included in our analysis, 48 deaths occurred over the follow-up period (median: 17.5 months). In a multivariable model including re-transplantation, physiologic MELD score (dichotomized at the sample median of 33), preoperative mechanical ventilation, previous malignancy, and HCV, LAVI was not a statistically significant predictor of mortality (HR: 0.99, p=0.99, 95% CI: 0.56, 1.77). Given that advanced liver disease is associated with cirrhotic cardiomyopathy, we explored whether the effect of LAVI on mortality differed as a function of MELD score. In a multivariable model including the covariates listed above, there was a statistically significant interaction between LAVI and MELD score (p=0.007).

Specifically, for patients with MELD scores ≥ 33, LAVI ≥ 28 ml/m^2 was associated with increased mortality (HR=2.4, p=0.032, 95% CI 1.1, 5.4). However, for patients with MELD scores < 33, LAVI was not associated with mortality (HR: 0.44, p=0.08, 95% CI 0.18, 1.1). The C-statistic for the model including LAVI and the interaction was 0.73, statistically significantly greater than the C-statistic of 0.67 for the model excluding these terms, thus demonstrating an improvement in the predictive ability of that model.

Discussion: This is the first study to examine the effect of LAVI as a predictor of post-liver transplant mortality using a multivariable model. We demonstrated that LAVI had a significant impact on mortality among patients with high MELD scores, whereas this effect was not observed among patients with lower MELD scores. Liver transplant recipients with high LAVI values and high MELD scores may represent patients with advanced cirrhotic cardiomyopathy who may be at an increased risk of postoperative mortality. This may have important consequences for the selection of liver transplant recipients.

The thesis of Brent David Ershoff is approved.

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2016

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Abstract

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who may be at an increased risk of postoperative mortality. This may have important consequences for the selection of liver transplant recipients.

Background

Cardiac complications are the leading cause of long-term non-graft related mortality following liver transplantation.[1] Death secondary to heart failure has been observed in 7.3%[2] of transplant recipients, and cardiac morbidity in the post-transplant period has a high prevalence with as many as 70 percent of patients experiencing at least one cardiovascular event.[3] With current liver transplant recipients being older, having more advanced end stage liver disease (ESLD), and having a greater number of comorbidities compared to those in the pre-MELD era[4], cardiac complications may become an even more significant cause of post-transplant mortality.

Patients with proven coronary artery disease, arrhythmias, and structural heart disease have worse outcomes after liver transplantation.[5,6,7] Perhaps this is not surprising given that cirrhosis has long been known to be associated with cardiovascular changes including a decrease in systemic vascular resistance with a consequent increase in cardiac output,[8] cardiac chamber enlargement[9], electrophysiologic changes including prolongation of the QT interval,[10] impaired systolic response reserve,[11] and diastolic dysfunction.[12] In 2005, the World Congress of Gastroenterology proposed a working definition of cirrhotic cardiomyopathy, which is a spectrum of cardiovascular changes associated with ESLD including diastolic dysfunction, systolic dysfunction, cardiac structural changes, electrophysiologic abnormalities, and abnormal serum markers.[13,14] Diastolic dysfunction, one of the components of cirrhotic cardiomyopathy, has received increased attention given that many studies have demonstrated an association between measures of diastolic dysfunction and mortality in multiple populations.[15]

While there are various echocardiographic measures of diastolic dysfunction, most rely on measurements of transmitral inflow velocities which are load sensitive (i.e. they change with respect to preload and afterload), and therefore, reflect short term changes in left ventricular filling pressures.[16,17,18] Left atrial volume index (LAVI) is an emerging echocardiographic measure of diastolic dysfunction that has been shown to be a significant predictor of cardiovascular morbidity and all-cause mortality in several populations,[17,19,20,21,22,23] and unlike many other echocardiographic measures of diastolic function, is not load dependent. LAVI is defined as the left atrial volume divided by body surface area, with high values considered abnormal. While several cutoff values for abnormal LAVI have been proposed, the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group defined LAVI > 28 ml/m^2 as abnormal.[24]

In the absence of primary atrial disease, mitral valve pathology, and overt left ventricular systolic dysfunction, LAVI it thought to be a more stable measurement of diastolic dysfunction as it may express long-term exposure to elevated left-ventricular filling pressures.[16,17,18] While several studies have found diastolic dysfunction prior to liver transplantation to be associated with increased mortality,[25,26,27] these studies often used vague or old definitions of diastolic dysfunction, all of which relied on transmitral inflow velocities.[25, 26, 27,28] To date, there has been only one study evaluating the association between LAVI and mortality in liver transplant recipients. In a retrospective study, Dowsley et al found that patients with LAVI ≥ 40 ml/m^2 had a 2.9 fold increase in the risk of heart failure following transplantation, and in an unadjusted analysis, an increased risk of mortality at one year post-transplantation.[26]

While cardiac morbidity and mortality are quite prevalent following liver transplantation, there is a dearth of research in the development of multivariable risk models for mortality that include cardiac specific risk factors. Several authors have developed multivariable predictive models of mortality using UNOS registry data. One of the more commonly used risk models is the Scientific Registry of Transplant Recipients (SRTR) which publishes yearly risk adjusted models for 1-year and 3-year survival post liver-transplantation. Despite the high prevalence of cardiac morbidity and mortality in this population, there are no cardiac specific risk factors included in the SRTR survival models. To build on this, we conducted a retrospective observational cohort study to evaluate the effect of LAVI on post-operative mortality. The aims of this study were to determine whether LAVI is an independent predictor of post-operative mortality following liver transplantation, and to determine whether LAVI improves the ability to predict mortality beyond known risk factors.

Methods

Study design: After investigational board review approval was obtained (IRB# 12-001841), we conducted a retrospective observational cohort study. Our study sample included all patients greater than or equal to 18 years of age who underwent liver transplantation at the University of California, Los Angeles between July of 2011 and June of 2014. Only patients whose preoperative transthoracic echocardiogram was performed at UCLA were included in the sample, as LAVI measurements were frequently not available from the echocardiogram reports from outside institutions. Patients who were listed as status 1a as well as those who underwent combined cardiac and liver transplantation procedures were excluded from the sample as these subgroups likely possessed pathology distinct from that of the remaining subjects. Of the 285 patients who met inclusion criteria, LAVI was only available on 254 subjects, which comprised the sample for which all analyses were performed.

Measurements: The primary outcome variable was time until all- cause post-transplant mortality, which was ascertained by querying the UNOS database. For patients who survived during the follow-up period, their observations were censored on their last date of follow-up. The primary predictor variable was left atrial volume index (LAVI) which is defined as the left atrial volume as measured by transthoracic echocardiography divided by body surface area which was calculated using the Mostellar formula.[29] As some patients had multiple transthoracic echocardiograms (TTE) performed in the pre-transplant period, the pre-operative LAVI value that was recorded most proximal in time to transplantation was used in the analysis. As described in detail elsewhere, left atrial volume was measured by using the biplane area-length method.[24]

Briefly, left atrial area was measured in the 2-chamber (A1) and 4-chamber (A2) views, and the shortest length from the 4-chamber and 2-chamber views was measured as well (L). The left atrial volume was approximated by (0.85*A1*A2)/L. All echocardiograms were read by board certified cardiologists. LAVI was treated as a dichotomous variable with the cut-point defined by the sample median, which was similar to the cut-point defined by the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group's classification of LAVI > 28 ml/m^2, which is considered abnormally high.[24]

Measurements on recipient and donor variables that are known to be independently associated with post-operative mortality from the SRTR database were collected on all subjects by querying the UNOS database. Recipient characteristics included age, height, weight, sex, race, preoperative dialysis, preoperative mechanical ventilation, history of diabetes, history of previous malignancy, previous abdominal surgery, infection with HCV, presence of portal vein thrombosis, and previous liver transplantation. Donor characteristics included age, race, height, partial/split donor organ, donation after cardiac death, donor location (regional or national), donor cause of death, and cold ischemia time (CIT). The physiologic MELD score, that is scores that do not take into account MELD exception points, were calculated using the preoperative data most proximal in time to transplantation. MELD score was treated as a dichotomous variable with the cut-point being the sample median. There was no missing data for recipient variables, and for donor variables, only four of 254 subjects had missing values for CIT and donor height. Left ventricular ejection fraction, a variable not included in the SRTR database, was abstracted from the echocardiogram report. For values that were reported as a range, e.g. 60-65%, the midpoint, i.e. 62.5%, was the value used in the analysis. The presence of coronary

artery disease, which was not included in the SRTR database, was defined as being positive if a patient had ≥ 50% stenosis of one or more vessels on coronary angiography, and as negative if the patient had < 50% stenosis on coronary angiography or a negative stress test. Patients with a history of a previous coronary intervention were categorized as having coronary artery disease.

Statistics: Descriptive statistics for continuous variables were presented as means ± standard deviations or as medians (interquartile ranges) for variables with skewed distributions, and as proportions for categorical variables. Comparisons of recipient and donor risk factors between those with high and low values of LAVI were performed using the independent samples t-test and the Wilcoxon rank-Sum test (for variables with skewed distributions) for continuous variables, and Fisher's exact test was used for categorical variables. Multivariable Cox regression was used to model the association between various predictors and time to post-operative mortality. A backwards stepwise selection procedure was used (with p=0.15 as a cut-point)**,** and LAVI, MELD, and an LAVI by MELD score interaction was forced into the model. A p-value less than 0.05 was considered statistically significant. The proportionality assumption was verified by using the method of time varying covariates and by the examination of Schoenfeld residuals.

Model discrimination was assessed by calculation of Harrell's C-statistic. To determine whether the addition of the set of variables LAVI and the LAVI by MELD score interaction improved the ability to predict mortality beyond known risk factors, we determined whether the addition of these variables led to a statistically significant increase in the C-statistic. To evaluate this, we

performed a Monte Carlo simulation whereby the true LAVI was replaced by a random noise variable which was generated from sampling from a standard normal distribution. The multivariable Cox regression was rerun replacing LAVI and the LAVI by MELD score interaction with the noise based LAVI and its interaction with MELD score, respectively. The C-statistic for this model was calculated and the simulation was repeated for a total of 2000 times. Based on these runs, we constructed the sampling distribution of the C-statistic under the null hypothesis (i.e. that the addition of LAVI and the LAVI by MELD score interaction did not increase the predictive ability of the model), and compared the observed value of the C-statistic to those derived from the simulation. From this, a p-value was calculated for testing whether the addition of LAVI and the LAVI by MELD score interaction led to a statistically significant increase in the C-statistic. All statistical analyses were performed using Stata version 13.

Results

The median LAVI was 27 ml/m^2 with an interquartile range of 19.6 ml/m^2 to 34.8 ml/m^2. Descriptive statistics for recipient variables are presented Table 1 stratified by LAVI ≥ 28 ml/m^2 and LAVI < 28 ml/m^2. The sample was notable for the advanced age of the recipients with a sample median of 58.5 years, the severity of advanced ESLD with a median physiologic MELD score of 33, and the prevalence of multi-organ dysfunction with 43.7% of patients requiring preoperative dialysis and 23.2% requiring preoperative mechanical ventilation. Donor characteristics including donor age, donor height, donor race, donor cause of death, donation after cardiac death, donor location, partial/split allograft, donor risk index, and CIT were compared between patients with LAVI ≥ 28 ml/m^2 and LAVI < 28 ml/m^2. Only CIT differed significantly across levels of LAVI, with patients with low LAVI values having a mean CIT of 462 minutes compared to those with high LAVI values having a mean CIT of 430 minutes (p=0.036).

LAVI as a predictor of mortality: To address our first aim, we investigated whether LAVI was an independent predictor of post-operative mortality. A total of 48 patients died during the follow-up period with a median follow-up time of 17.5 months. In a multivariable model that included re-transplantation, history of previous malignancy, HCV status, and preoperative mechanical ventilation, LAVI was not associated with mortality (HR: 0.998, p=0.99, 95% CI: 0.56, 1.77). Given that patients with high MELD scores are known to be at an increased risk for cirrhotic cardiomyopathy, we examined whether the effect of LAVI on mortality differed as a function of MELD score.

To model this effect, we included an LAVI by MELD score interaction term in the Cox regression model. In a multivariable model that included re-transplantation, history of previous malignancy, HCV status, and preoperative mechanical ventilation, there was a statistically significant LAVI by MELD score interaction (p=0.007)**.** Specifically, for patients with a MELD score less than 33, higher LAVI values ($\geq 28 ml/m^2$) were not associated with mortality (HR: 0.44, p=0.08, 95% CI 0.18, 1.1). Among patients with a MELD score ≥ 33, however, higher LAVI values were associated with increased mortality (HR=2.4, p=0.032, 95% CI 1.1, 5.4). The hazard ratio estimate for this LAVI strata was calculated by exponentiating the linear combination of the LAVI and MELD coefficients (see Table 2). The regression model which included the LAVI and the LAVI by MELD score interaction (the full model), fit significantly better than the model without these terms (the reduced model) as assessed by the likelihood ratio test (p=0.018). A comparison of models using the C-statistic measure will follow below.

To graphically appreciate this interaction, patients were categorized into one of four strata defined by the combination of LAVI values and MELD scores, with the median values of LAVI and MELD score serving as the cut-points to determine group membership. For example, patients with LAVI < 28 ml/m^2 and MELD score < 33 fell into one stratum whereas those with LAVI < 28 ml/m^2 and MELD score ≥ 33 occupied another stratum. Figure 1 displays Kaplan-Meir survival curves for post-liver transplant mortality for each of the four strata defined above. Subjects in the stratum defined by a combination of a high MELD score and a high LAVI value (i.e. MELD score ≥ 33 and LAVI $\geq 28 ml/m^2$) had decreased survival compared to those within the other strata.

Table 2 provides the hazard ratios, p-values, and 95% confidence intervals for each of the predictors in the multivariable Cox regression model. Consistent with previous research, independent predictors of mortality included HCV status, preoperative mechanical ventilation, and re-transplantation. Patients who were HCV positive had a hazard rate of mortality that was 2.1 times greater than those who were HCV negative (p=0.016, 95% CI: 1.2, 3.9). Patients who underwent re-transplantation had a hazard rate of mortality that was 4.1 times greater than those who were undergoing their first liver transplant (p=0.026, 95% CI: 1.2, 14.4). Those who were intubated preoperatively had a hazard rate of mortality that was 2.1 times greater than those who were not intubated preoperatively (p=0.023, 95% CI 1.1, 4.1). Contrary to previous data, in this sample, a history of previous malignancy was associated with improved survival with those having a history of previous malignancy having a 64% reduction in the hazard rate of mortality (p=0.01, 95% CI 0.17, 0.78). As mentioned above, CIT was associated with LAVI in a univariate analysis, but was not selected as a variable via the backwards selection procedure. Forcing the inclusion of CIT into the Cox regression model did not induce any relevant changes to any of the parameter estimates, nor did it qualitatively change their statistical significance.

LAVI as an improvement in the prediction of mortality: To address our second aim as to whether LAVI improved the ability to predict mortality beyond other known risk factors, we compared the C-statistic for the model which included LAVI and the LAVI by MELD score interaction (the full model) to the C-statistic for the model without these terms (the reduced model). The C-statistic for the full model was 0.73, whereas the C-statistic for the reduced model was 0.67. As the inclusion of additional variables in a model often increases the C-statistic by chance alone, we performed a Monte Carlo simulation to estimate the probability that the higher

C-statistic for the full model was due to probability alone. Based on the results of the simulation, the C-statistic for the full model was greater than that of the reduced model (p=0.004), suggesting that LAVI improves the ability to predict mortality (see Figure 2 for the frequency distribution of C-statistics under the null hypothesis as generated by the Monte Carlo simulation).

Discussion

This is the first study to evaluate the effect of LAVI on post-liver transplant mortality using a multivariable model. We found evidence of a statistically significant interaction between LAVI and MELD score such that the effect of LAVI on postoperative mortality differed as a function of MELD score. While LAVI alone (i.e. without consideration of an interaction effect) was not associated with mortality, it is important to note that the confidence interval of the hazard ratio for LAVI was wide (0.56, 1.77), and therefore, the possibility of a clinically significant effect of LAVI, alone, cannot be excluded. The decision to test an LAVI by MELD score interaction was based on prior knowledge of the association between advanced ESLD (as reflected by higher physiologic MELD scores), and cirrhotic cardiomyopathy.[30] Given that LAVI is known to be a stable and accurate measure of diastolic dysfunction[16, 17, 18], we hypothesized that elevated LAVI may serve as a marker of cirrhotic cardiomyopathy among the subset of patients with high MELD scores. The results of this study suggest that high LAVI values ($\geq$ 28 ml/m^2) were only associated with increased mortality among patients with high MELD scores ($\geq$ 33), but not among those with lower MELD scores. This suggests that patients with the combination of both high MELD scores and high LAVI values may be at a particularly high risk of post-operative mortality. The combination of left atrial enlargement in the setting of advanced ESLD may be a marker of severe cirrhotic cardiomyopathy.

Given that LAVI is a known risk factor for morbidity and mortality in many populations[17, 19 , 20 , 21, 22, 23], it is interesting that for patients with lower MELD scores, LAVI was not associated with mortality. Left atrial enlargement frequently occurs in the general population from diastolic

dysfunction caused by etiologies other than cirrhotic cardiomyopathy. Left atrial enlargement attributable to those other etiologies may not be associated with mortality to the same degree as it is with left atrial enlargement secondary to cirrhotic cardiomyopathy. Furthermore, as the median follow-up time of this study was 17.5 months, mortality from diastolic dysfunction of other etiologies may not have had time to be observed, whereas mortality related to cirrhotic cardiomyopathy may manifest earlier in the post-transplant period.

Other significant predictors of increased post-operative mortality identified were HCV status, pre-operative mechanical ventilation, and re-transplantation. As reported in the SRTR database, these variables are associated with post-operative mortality and have particularly high hazard ratios of mortality associated with them.[31] Interestingly, the presence of previous malignancy, a variable identified in the SRTR database as being associated with mortality, was found to be associated with a decreased risk of mortality in this study. This finding may be due to the fact that mortality attributed to previous malignancy often does not occur early in the follow-up period, and in this study, the follow-up time was relatively short. There are several other predictors of mortality in the SRTR database that were not selected for inclusion in our model. As there were only 48 deaths during the study, only so many variables could be chosen without significant overfitting. Sensitivity analyses were performed whereby various predictors were either added or deleted from the model to determine whether the results were qualitatively changed. As an example, CIT may have been a confounder as it is a variable known to be associated with mortality in the SRTR database, and in our study, was associated with LAVI. In no cases, did the addition or deletion of a covariate change the nature of the effect of LAVI on mortality, and in all cases the interaction effect remained statistically significant.

To date, there has been only one study evaluating the effect of LAVI on post-liver transplant mortality. In a retrospective study, Dowsley et al found that LAVI $\geq$ 40 ml/m^2 was associated with an increased risk of mortality with only 54% surviving at one year compared to 82% surviving in those with LAVI < 40 ml/m^2 [26]. In contrast to their results, we found evidence of an association between LAVI and mortality only among patients with high MELD scores ($\geq$ 33), but not among those with lower MELD scores. In Dowsley's study, the mean MELD score was 18.3 for patients with LAVI < 40 ml/m^2 and 22.3 for those with LAVI $\geq$ 40 ml/m^2, indicating that patients in our sample had more advanced ESLD with a median MELD score of 33. Differences in methodology may explain the differences in our study's findings, with this study modeling mortality using a multivariable Cox regression model, and Dowsley's providing only unadjusted estimates for survival. Their study also only included patients who had post-operative echocardiograms performed, which had the potential to induce selection bias.

In addition to showing that LAVI, in the context of an LAVI by MELD score interaction, was an independent predictor of mortality, we demonstrated that the inclusion of LAVI as a predictor in a multivariable risk model improved the ability to predict mortality beyond other known risk factors. The addition of LAVI and the LAVI by MELD interaction to a multivariable Cox regression model increased the C-statistic from 0.67 to 0.73, which was a statistically significant improvement in the discriminatory ability of the model. As the number of patients on the liver transplant waiting list exceeds the numbers of suitable donor organs, it is imperative to develop predictive models of post-operative mortality so that organs are offered to those with a reasonable probability of post-operative survival. Recently, Petrowsky et al created a futility index based on a multivariable risk model that predicted the probability of post-operative

mortality, and found that recipients with high MELD scores and elevated cardiac risk, pre-transplant septic shock, or high levels of comorbidities were at particularly high risk of early post-operative mortality.[6] Interestingly, they found that those with cardiac risk factors were at particularly high risk.

While we are the first to examine the association between LAVI and post-liver transplant mortality using a multivariable model, a number of limitations of this study deserve mention. First, given that this was an observational study, there exists the possibility that the association between LAVI and post-operative mortality was due to confounding. While several covariates were measured, there exists the possibility that there were unmeasured confounders that induced the observed association between LAVI and mortality. As this was a retrospective study, there were limitations with respect to the measurement of our primary predictor. While all patients received a preoperative TTE, the timing of the echocardiogram with respect to its proximity to transplantation differed across patients, with some recipients being imaged on the day of transplantation and others up to a year prior to transplant. It is possible that had the echocardiograms been performed more proximal to the time of transplant, the LAVI measurement would have been different. As LAVI is defined as the left atrial volume divided by BSA, and given that patients with ESLD often have fluctuating body weights due to changes in volume status (e.g. secondary to ascites), LAVI may not be as stable of a marker of diastolic dysfunction in this population. While there are clear disadvantages to using load dependent measurements of diastolic dysfunction such as transmitral inflow velocities, there may be limitations to using LAVI as a marker of diastolic dysfunction in the liver transplant population. Other load independent measures of diastolic dysfunction such as tissue Doppler should be

investigated in this population. While time to mortality data was ascertained from the UNOS database, given the retrospective nature of the study, we were unable to collect accurate and complete data regarding the cause of death and the incidence of cardiac morbidity.

As liver transplant recipients become older, have more advanced ESLD, and have a higher frequency of medical comorbidities including cardiac disease, the importance of creating multivariable risk models that include cardiac risk factors is crucial. While death secondary to cardiac complications is the leading cause of long term non-graft related mortality following liver transplantation, the UNOS registry does not collect data on cardiac specific risk factors. Given the association between ESLD and cardiac dysfunction, identifying patients with cirrhotic cardiomyopathy may better risk stratify patients and avoid futile transplantation, and may also allow for targeted therapy against cardiac dysfunction in the perioperative period. Future studies that prospectively measure cardiac risk factors and prospectively collect data on cardiac morbidity and mortality are warranted.

Chapter 2: Statistical Appendix

Monte Carlo Simulation

Motivation: The second aim of this study was to determine whether the inclusion of LAVI as a predictor in the multivariable Cox regression model improved the ability to predict mortality beyond known predictors. One measure of a Cox regression model's discriminatory ability is Harrell's C-statistic which ranges from 0.5 to 1, with higher values indicating better discrimination. While predictors that are added to a model may have statistically significant coefficients, they may not actually improve the predictive ability of the model. For nested models, one way to compare models is via the likelihood ratio test, which compares the goodness of fit of a full model to that of the reduced model which includes only a subset of the predictors of the full model. In this study, we found a statistically significant interaction between LAVI and MELD score in a multivariable Cox regression model that included LAVI, MELD score, HCV status, preoperative mechanical ventilation, history of previous malignancy, and re-transplantation status. Given that the reduced model (the model without LAVI and the LAVI by MELD interaction) is nested within the full model, the likelihood ratio test is an appropriate method to compare models. The likelihood ratio test showed that the inclusion of LAVI and its interaction with MELD score fit better than the reduced model with a p-value of 0.018.

Here I explored an alternative method to compare the C-statistics for two models which does not rely on asymptotic theory. As the probability distribution of the likelihood ratio is often difficult to determine, Wilk's Theorem is used which states that as the sample size approaches infinity,

the test statistic -2*log likelihood ratio of a nested model is asymptotically distributed as chi-square with degrees of freedom equal to the difference in the dimensionality of the full and reduced model. By performing the following Monte Carlo simulation, I compared whether the model with LAVI and its interaction with MELD score had a statistically significantly higher C-statistic than that from the model without these terms. Simply comparing the C-statistic for the model without LAVI and its interaction with MELD score to the reduced model would not be a legitimate comparison, as the addition of 2 more parameters, namely LAVI and the LAVI by MELD score interaction, may have increased the C-statistic by chance alone.

Procedure: I first produced an approximation of the distribution of the C-statistic under the null hypothesis, that is, under the assumption that the inclusion of the set of predictors LAVI and its interaction with MELD score does not add predictive ability to the model. I then determined, at which percentile of the null distribution, the C-statistic for the model fit to the original data lies. If this percentile were greater than 0.95, the null hypothesis would be rejected (at $p<0.05$), and I would conclude that full model had better discriminatory ability than the reduced model.

First, a variable X was generated which was a vector of size N (where N is the number of subjects in the dataset) whose values were selected from randomly sampling from a standard normal distribution. Another variable "Inter", was generated which was defined as the product of the variable MELD score and X. These two variables are in essence a random noise representation of LAVI and the LAVI by MELD score interaction in the original model. Since

these variables were generated by random sampling from the standard normal distribution, it was expected that they would add no predictive value to the model.

The simulation algorithm was as follows: The original dataset (S_0) was loaded which includes the following predictor variables: HCV, MELD score, previous malignancy, re-transplantation, preoperative mechanical ventilation, LAVI, and the LAVI by MELD score interaction (LAVI*MELD). Variables LAVI and LAVI*MELD were deleted. A variable called X was generated, which was a vector of values drawn randomly from a standard normal distribution. A variable "Inter" was generated which was the product of the variable X and MELD score. The resultant dataset was called S_1 as this was the first simulated dataset. Next, a Cox regression model was fit with the following variables: HCV, MELD score, previous malignancy, re-transplantation, preoperative mechanical ventilation, X, and Inter. The C-statistic for this model, named C_1, was calculated, and this value was stored. S_0 was then reloaded, and this procedure was repeated a total of 2000 times generating datasets S_2, S_3,…S_{2000}, along with the corresponding C-statistics C_1, C_2,…C_{2000}. This distribution of 2000 C-statistics is the distribution under the null hypothesis that LAVI along with the LAVI by MELD score interaction do not provide additional predictive ability to the Cox regression model. The cumulative distribution function (CDF) of C, evaluated at the C-statistic derived from the Cox regression model fit to the original data set, is the probability of observing a value less than C under the null hypothesis. Therefore, 1-CDF is the probability of observing the C-statistic, or one higher than this, under the null hypothesis.

The C-statistic for the Cox regression model with all 7 variables including LAVI and the LAVI by MELD score interaction fit using the original dataset was 0.7256. Figure 2 is a histogram of the distribution of the C-statistics from this Monte Carlo simulation with a vertical line at x=0.7256. 1-CDF is 0.004. Therefore, I rejected the null hypothesis at a p value of 0.004, and concluded that the addition of LAVI and the LAVI by MELD score interaction improved the ability to predict mortality. Of note, 86.35% of simulated C-statistics were greater than 0.6728, the C-statistic for the reduced model. This demonstrates that the addition of a random noise variable to the model, will on average, increase the C-statistic.

Bootstrap

Motivation: When a model is fit using the sample data, the estimate of the predictive ability of that model will be greater than how the chosen model will perform on another sample drawn from the same population. This is known as overfitting, and as the number of parameters included in the model increases, overfitting can occur. For small datasets with a large number of predictors included in the model, this can become a serious problem when the goal is prediction. There are various methods to estimate how the chosen model will perform on an external dataset. One option is to develop the model using a sample, and then determine how well that model performs on an external dataset. Unfortunately, it is often difficult to collect an external dataset as it may be expensive or unfeasible. Another option is to develop the model on a training dataset and then test the performance of that model on a validation set. A problem with this approach is that since some data is held out from the training set, power is lost. One option, which is the subject of this discussion is internal validation. Two methods of internal validation are k-fold cross validation and bootstrapping. Here I will discuss how I used bootstrapping as a method of internal validation.

Theory: Efron described an enhanced bootstrap method for providing nearly unbiased estimates of the model's performance on another sample. Instead of the simple bootstrap procedure, where the test statistic is calculated on each subsample and averaged, the enhanced bootstrap procedure obtains an estimate of the optimism of the model performance. The optimism is the difference between the measure of model performance on the bootstrapped sample and that which is calculated when the model fit to the subsample is applied to the original data set. After the

optimism is estimated, it is subtracted from the estimate of the model performance on the original sample to obtain an estimate of the model performance on an independent sample.

Procedure: From the original data set of size N, a Cox regression model was fit using the following variables: LAVI, MELD score, LAVI by MELD score interaction, HCV status, preoperative mechanical ventilation, history of previous malignancy, and re-transplantation status. The C-statistic for this model was calculated and saved as C_{app}. Next, a sample of size N was drawn with replacement from the original dataset, and from this subsample, a model was fit using the parameters listed above. The C-statistic for this model, let's call it C_{boot}, was then stored. This model was then applied to the original data set and the C-statistic, let's call it C_{orig}, was stored. The difference between these two measures of model performance is the optimism. The difference between C_{boot} and C_{orig} was calculated and stored as the variable "optimism". This procedure was repeated 200 times and the estimates of optimism on each subsample were stored. Figure 3 is a histogram of the 200 optimism values that were calculated. The mean of the values of optimism was calculated, and this provided an estimate of the optimism of the model. This value was then subtracted from C_{app}, to provide an estimate of the C-statistic for the model if it were applied to an independent sample.

The C-statistic for the Cox regression model applied to the original data set was 0.7256. The estimate of the optimism using this procedure was 0.044. Therefore, the estimate of what the C-statistic would be on an independent sample is 0.7256-0.044 = 0.6816.

Exploration of Different Cut-points for LAVI and MELD Score

In the building of the multivariable Cox regression model, decisions had to be made regarding whether to treat the predictors as continuous variables or categorical variables. Dichotomizing a continuous variable may lead to reduced statistical power if the relationship is, in fact, linear. Dichotomizing a continuous variable, however, can sometimes ease the interpretability of the results. In this study, I had to decide how best to treat the two predictors, LAVI and MELD score, which in turn affected the nature of the LAVI by MELD score interaction.

LAVI has been treated as both a continuous variable as well as a categorical variable in the literature. Various dichotomous cut-points including 28 ml/m^2, 32 ml/m^2, 34 ml/m^2, and 40ml/m^2 have been used, and multilevel categorizations have been utilized as well. As we were evaluating an LAVI by MELD score interaction, we also had to decide whether to treat MELD score as a continuous or categorical variable. Figure 4 is a histogram of physiologic MELD scores. The bimodal nature of the data can be appreciated, with the lower mode due to the group of patients who received MELD exception points. The data were far from normal, and transformation of this variable to achieve a more normal distribution was not a valid option, so the variable was dichotomized and treated as a categorical variable. For this analysis, MELD score was dichotomized at the median which was 33. Other cut-points would also be reasonable and a sensitivity analysis was performed whereby the analysis was rerun with MELD score dichotomized at the sample 75th percentile of 39. In a model which evaluated the LAVI by MELD score (dichotomized at 39) interaction, the results were qualitatively unchanged and the p-value for the interaction was 0.005.

In another sensitivity analysis, LAVI was treated as a continuous variable. Figure 5 is a histogram of LAVI values. In a model that evaluated a LAVI (treated as a continuous variable) by MELD score (dichotomized at 33) interaction, the nature of the interaction was qualitatively unchanged and the p-value for the interaction was 0.044. Another model was examined whereby we evaluated the LAVI (treated as a continuous variable) by MELD score (dichotomized at 39) interaction, and the nature of the interaction was qualitatively unchanged with a p-value of 0.025. In one last sensitivity analysis, patients with previous malignancy were excluded so that the remaining patient's represented a group of patients who largely had no MELD exception points. A histogram of the MELD scores for the patients in this group is shown in Figure 6. In a model that evaluated an LAVI (treated as a continuous variable) by MELD score (treated as a continuous variable) interaction, the nature of the interaction was qualitatively unchanged and the p-value was 0.003. One disadvantage of presenting a continuous by continuous interaction is that the results are difficult for the reader to interpret. In this section, I have shown that the results of the analysis are robust. Whether the primary predictors are treated as continuous or categorical variables, and regardless of exactly where the cut-point in the dichotomization lies, the results are qualitatively the same.

Figures and Tables

Table 1: Clinical and Demographic Characteristics of Recipients

	All	LAVI < 28 ml/m^2 (n=130)	LAVI ≥ 28 ml/m^2) (n=124)	p-value
Age (years)	58.5 (51-63)	57.5 (50-63)	59 (52-64)	0.22
Sex (Male)	156 (61.4%)	82 (63.1%)	74 (59.7%)	0.61
Recipient Height (cm)	168.0 ± 10.9	168.3 ± 10.7	167.6 ± 11.1	0.58
Recipient Weight (KG)	77.7 ± 19.6	77.9 ± 19.5	77.5 ± 17.6	0.85
Physiologic MELD	33 (15-39)	32 (12-39)	34 (19-39.5)	0.13
CAD	26 (10.2%)	15 (11.5%)	11 (8.9%)	0.54
Diabetes	65 (25.6%)	32 (24.6%)	33 (26.6%)	0.77
Previous Malignancy	102 (40.2%)	56 (43.1%)	46 (37.1%)	0.37
HCV	98 (38.6%)	49 (37.7%)	49 (39.5%)	0.80
Abdominal Surgery	111 (43.7%)	49 (37.7%)	62 (50.0%)	0.058
PVT	40 (15.8%)	20 (15.4%)	20 (16.1%)	0.99
LVEF	62.5 (60-67.5)	62.5 (60-67.5)	62.5 (57.8-67.5)	0.56
Dialysis	111 (43.7%)	56 (43.1%)	55 (44.4%)	0.90
Intubated	59 (23.2%)	28 (21.5%)	31 (25.0%)	0.55
SLKT	25 (9.8%)	9 (6.9%)	16 (12.9%)	0.14
Redo	6 (2.4%)	3 (2.3%)	3 (2.4%)	0.99
Black	10 (3.9%)	6 (4.6%)	4 (3.2%)	0.75

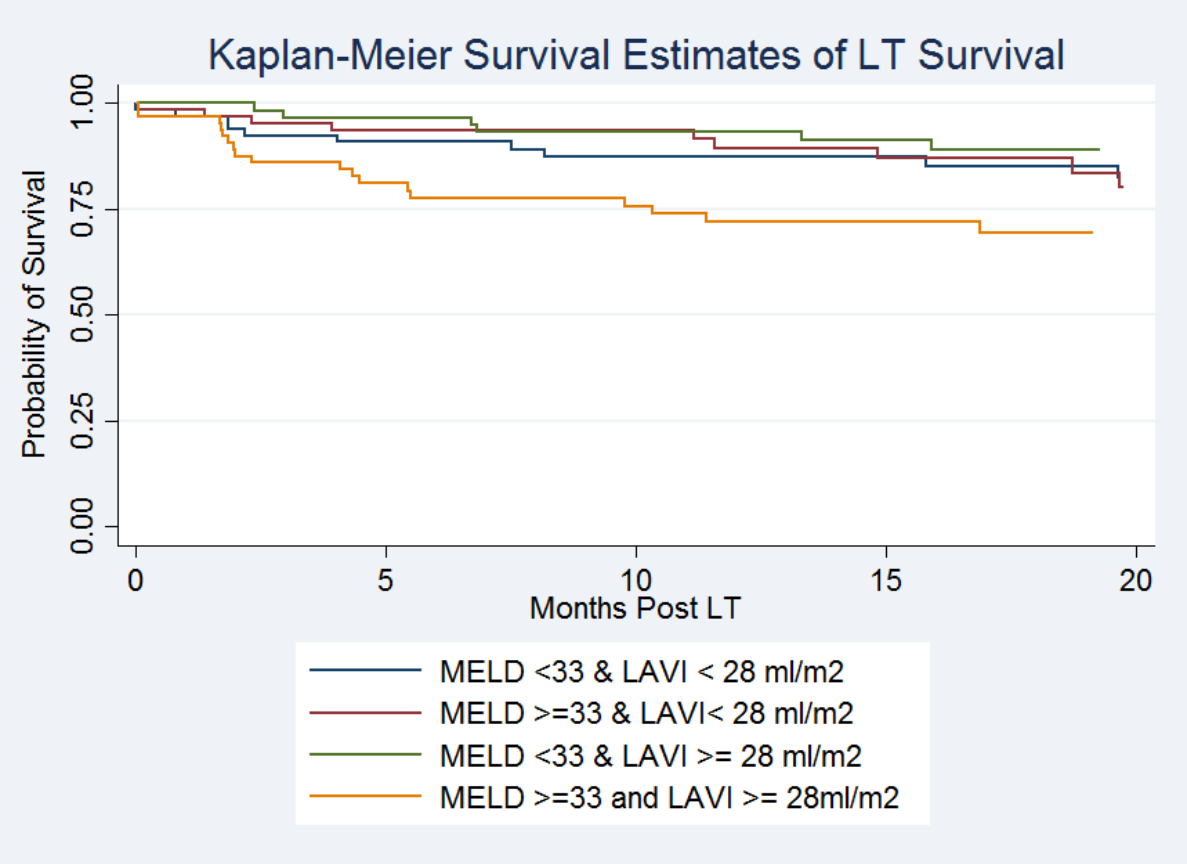
Descriptive statistics for demographic and clinical characteristics of recipient variables are shown. Continuous variables are presented as mean ± SD or as median (interquartile range) for skewed data. Categorical variables are presented as number (percentage). Statistics are provided for the entire sample as well as stratified by LAVI $\geq$ 28 ml/m^2 and LAVI < 28 ml/m^2. P-values for the measure of association between the recipient variable and LAVI are provided. Comparisons for continuous variables were performed using the independent samples t-test or the Wilcoxon rank sum test for skewed data. Comparisons for categorical variables were performed using Fisher's exact test. MELD = Model for End-Stage Liver Disease; CAD = coronary artery disease; HCV = Hepatitis C Virus; PVT = portal vein thrombosis; LVEF = left ventricular ejection fraction; SLKT = simultaneous liver kidney transplant; Redo = re-transplantation.

Table 2: Hazard Ratios and Corresponding P-values and 95% Confidence Intervals for Predictors in the Multivariable Cox Regression Model

Predictor	Hazard ratio (95% CI)	P-value
HCV	2.1 (1.2, 3.9)	0.016
REDO	4.1 (1.2, 14.4)	0.026
Life Support	2.1 (1.1, 4.1)	0.023
Previous Malignancy	0.36 (0.17, 0.78)	0.01
MELD	0.34 (0.13, 0.91)	0.032
LAVI	0.44 (0.18, 1.1)	0.08
MELD*LAVI	5.4 (1.6, 18.3)	0.007

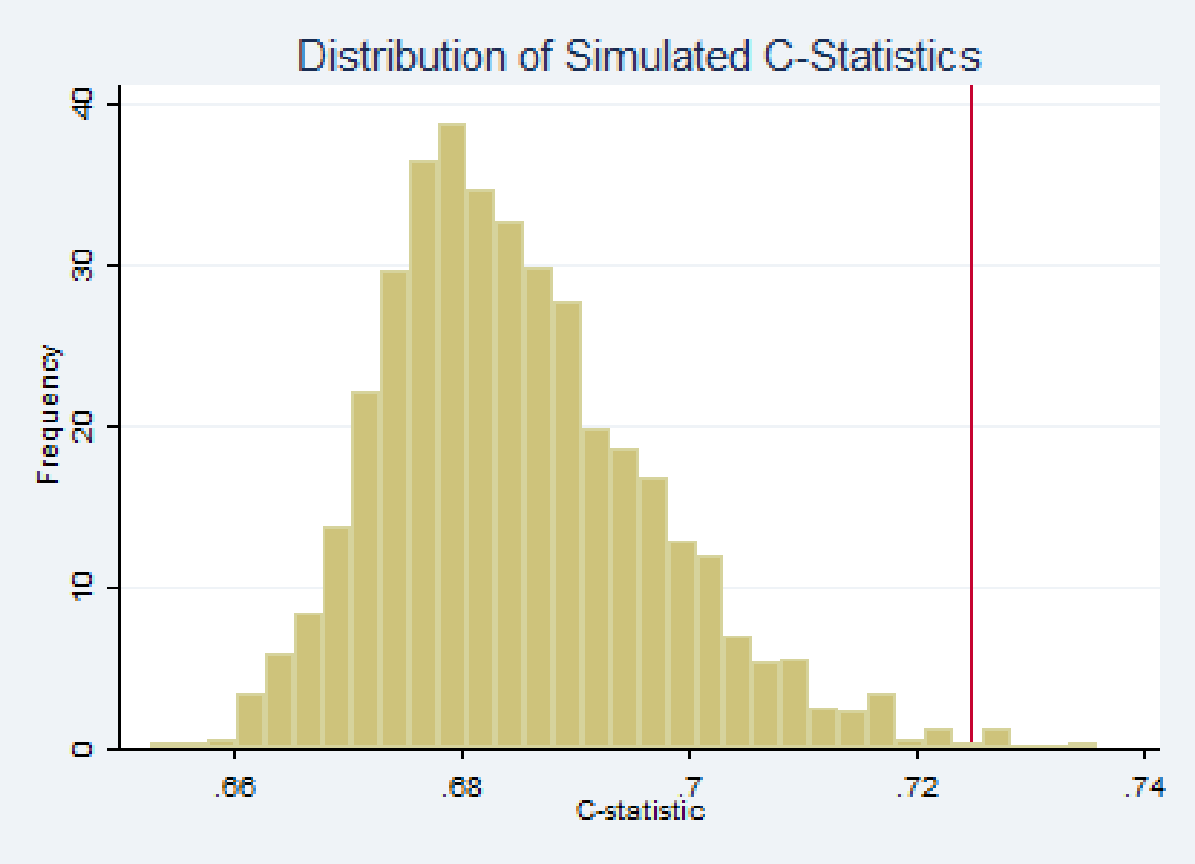
This table displays the predictors that were selected in the multivariable Cox regression model along with their corresponding hazard ratios, p-values, and 95% confidence intervals. MELD*LAVI represents the LAVI by MELD score interaction. As the model contains an interaction term, the interpretation of the LAVI hazard ratio estimate is the hazard ratio associated with LAVI $\geq$ 28 ml/m^2 compared to LAVI < 28 ml/m^2 among patients with a MELD score < 33. Similarly, the interpretation of the MELD hazard ratio estimate is the hazard ratio associated with MELD score $\geq$ 33 compared to MELD score < 33 among patients with an LAVI < 28 ml/m^2. In the text, an estimate of the hazard ratio associated with LAVI $\geq$ 28 ml/m^2 compared to LAVI < 28 ml/m^2 among patients with a MELD score $\geq$ 33 is provided (HR=2.4, p=0.032, 95% CI 1.1–5.4). The hazard ratio estimate is calculated by exponentiating the linear combination of the LAVI and MELD coefficients.

Figure 1: Kaplan-Meier Survival Estimates of Liver Transplant Survival



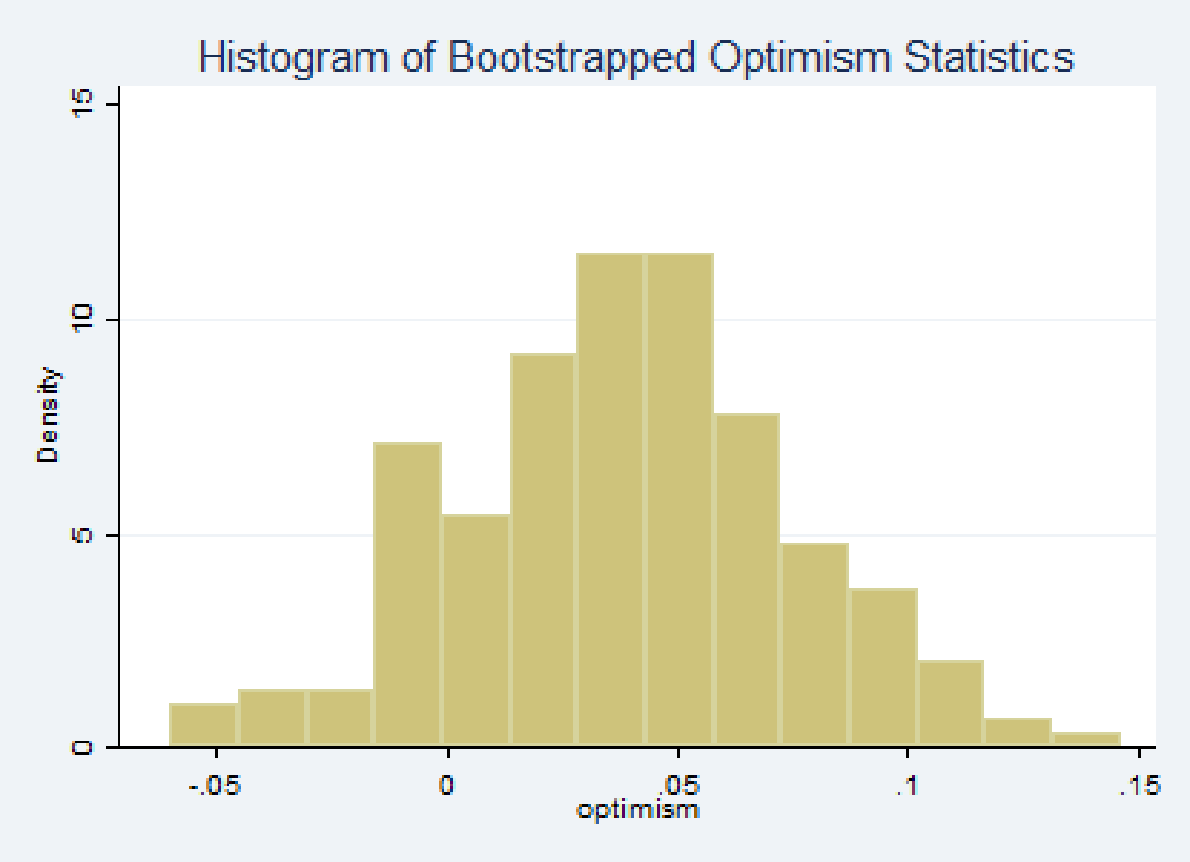
Kaplan-Meir survival curves of post-liver transplant survival for groups of patients defined by combinations of MELD scores and LAVI values. The group of patients with high MELD scores and high LAVI values have increased mortality. The group defined by MELD score < 33 and LAVI < 28 ml/m^2 had 66 patients with 13 deaths. The group defined by MELD score ≥ 33 and LAVI < 28 ml/m^2 had 64 patients with 9 deaths. The group defined by MELD score < 33 and LAVI ≥ 28 ml/m^2 had 60 patients with 8 deaths. The group defined by MELD score ≥ 33 and LAVI ≥ 28 ml/m^2 had 64 patients with 18 deaths. LT = Liver Transplant.

Figure 2: Distribution of Simulated C-Statistics from a Monte Carlo Simulation



The histogram depicts the frequency distribution of Harrell's C-statistics from 2000 Monte Carlo simulations whereby a Cox regression model was fit to simulated data where LAVI and the LAVI by MELD score interaction were replaced by a random noise variable (X) drawn from a standard normal distribution and by an X by MELD score interaction, respectively. This distribution represents the sampling distribution of the C-statistic under the null hypothesis that LAVI and the LAVI by MELD score interaction do not improve the ability to predict mortality. The red vertical line at Y=0.7256 illustrates the C-statistic from the model fit using the original data set. 99.6% of the C-statistics from the simulation were less than 0.7256, and therefore the null hypothesis that LAVI does not improve the ability to predict mortality was rejected at a p-value of 0.004.

Figure 3: Histogram of Bootstrapped Optimism Statistics



The histogram depicts the frequency distribution of optimism statistics derived from 200 bootstrapped subsamples. Most of the density of the histogram is greater than zero illustrating the fact that with respect to predictive ability, a model will usually perform better on the sample from which the model was fit. Only 16% of the optimism values were less than 0. The average of the optimism values provides the estimate of the optimism of the model. This value is subtracted from the C-statistic from the Cox regression model fit to the original data to provide an estimate of the C-statistic on an independent sample.

Figure 4: Histogram of Physiologic MELD Scores

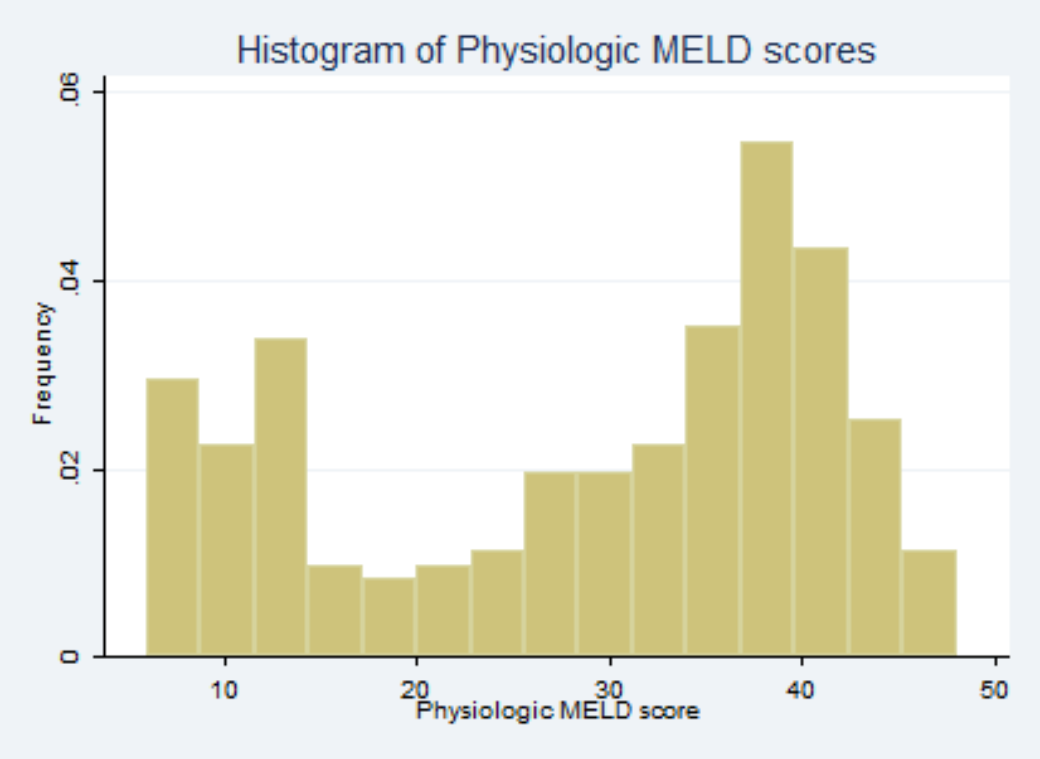


Figure 5: Histogram of LAVI Values

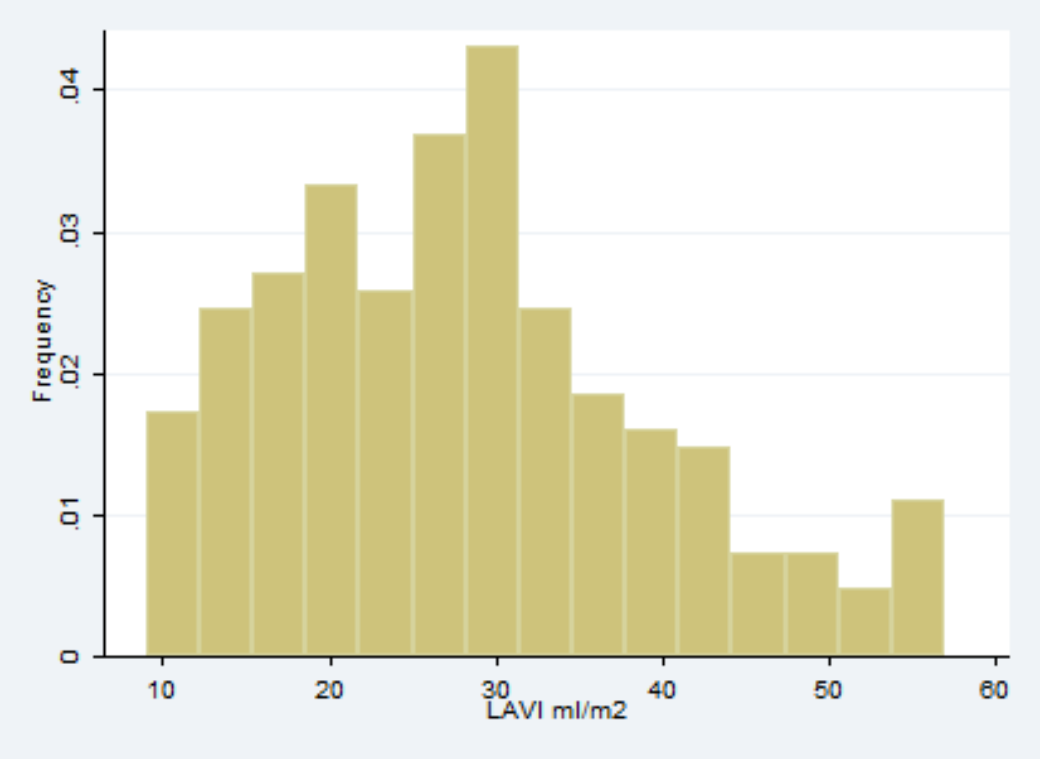
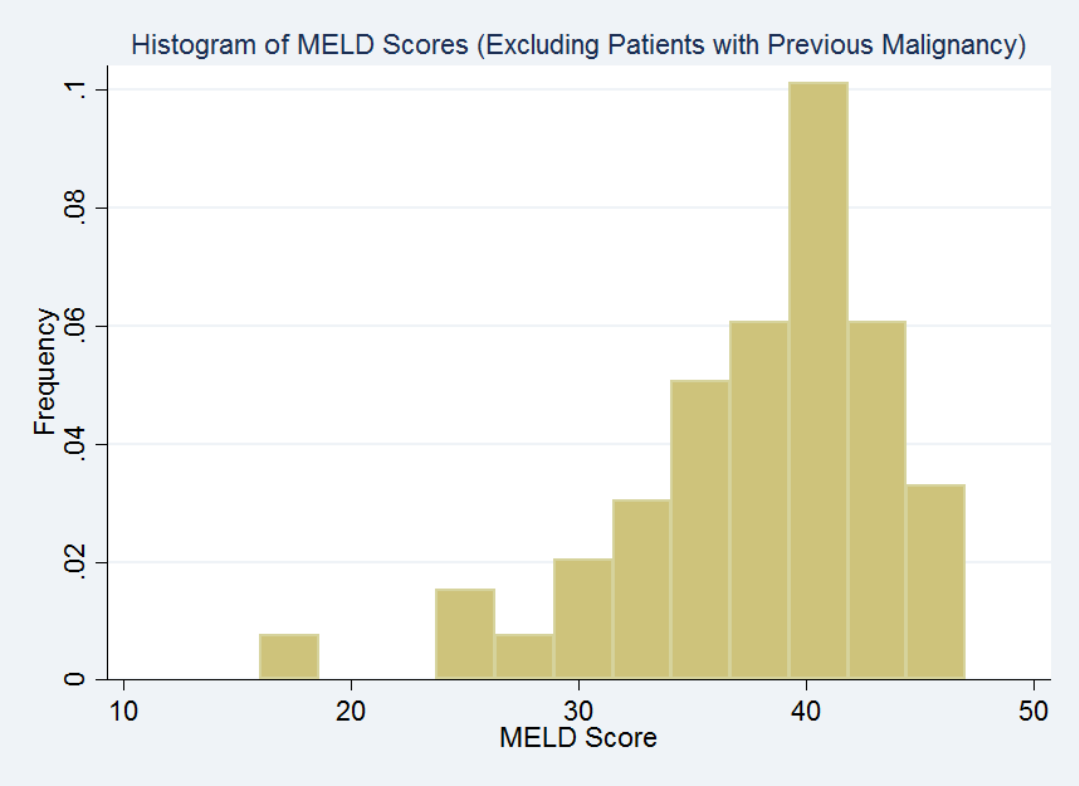


Figure 6: Histogram of MELD Scores



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