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UNIVERSITY OF CALIFORNIA

Los Angeles

The Association Between Pre-operative Mitral Tissue Doppler Velocity and
Survival after Orthotopic Liver Transplantation

A thesis submitted in partial satisfaction of the requirements
for the degree of Master of Science in Clinical Research

by

Jonathan Stanley Gordin

2016

ABSTRACT OF THE THESIS

The Association Between Pre-operative Mitral Tissue Doppler Velocity and Survival after Orthotopic Liver Transplantation

By

Jonathan Stanley Gordin

Masters of Science in Clinical Research

University of California, Los Angeles, 2016

Professor Marc Adam Suchard, Chair

Background: Diastolic dysfunction is a relatively common abnormality of the heart in the general population, and occurs at least as often in patients with advanced cirrhosis. Diastolic dysfunction is considered to be a hallmark finding in cirrhotic cardiomyopathy, which is a set of changes in the heart seen in advanced liver disease. We hypothesized that diastolic dysfunction, evidenced by abnormal lateral mitral annular tissue Doppler velocity, would negatively impact survival after liver transplant.

Methods: We performed a retrospective chart review of consecutive adult patients undergoing orthotopic liver transplantation at our institution with available pre-transplant echocardiograms over a ten-year period. The primary outcome was overall post-transplant survival. Cox proportional hazards model was utilized to evaluate the effect of diastolic dysfunction on survival, controlling for covariates previously known to be associated with survival. The benefit of inclusion of tissue Doppler velocity as a marker of diastolic dysfunction in the survival model was assessed with a likelihood ratio test as well Harrell's C-statistic and was compared with other previously reported diastolic parameters.

Results: Over the ten-year study period, 663 patients met inclusion criteria, 135 (20.4%) of whom had abnormal tissue Doppler velocities. Those with abnormal tissue Doppler tended to be slightly older, more often female, and have coronary disease or risk factors such as diabetes, hypertension, or renal disease. Otherwise, the abnormal and normal groups were well matched in etiology of cirrhosis, model for end-stage liver disease (MELD) scores, and markers of severity of illness including need for vasopressors, dialysis, and mechanical ventilation. After a median follow-up of 36.2 months, abnormal tissue Doppler velocity was shown to have a strong, negative association with survival (hazard ratio [HR] 1.91, $p < 0.0001$) in a model that included race, hepatitis C infection, need for dialysis and mechanical ventilation, recipient age, donor age, and MELD. Other variables that were found to be significant included hepatitis C infection (HR 1.46, $p = 0.01$) and need for dialysis (HR 1.37, $p = 0.049$).

Conclusions: In summary, we find that diastolic dysfunction, as evidenced by abnormal tissue Doppler velocity, is a common abnormality in liver transplant patients and is independently associated with decreased survival. Compared with clinical comorbidities included in the model, it was the most strongly associated with reduced survival, and performed better than other previously published diastolic parameters. Further studies are needed in a multi-center, prospective manner to confirm these findings and clarify the role of diastolic dysfunction in the pre-transplant evaluation of patients.

The thesis of Jonathan Stanley Gordin is approved.

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Acknowledgement

Jonathan Gordin is supported by the National Institutes of Health (NIH) Cardiovascular Scientist Training Program (T32 HL007895).

CHAPTER 1. MANUSCRIPT

ABSTRACT

Background: Diastolic dysfunction is a relatively common abnormality of the heart in the general population, and occurs at least as often in patients with advanced cirrhosis. Diastolic dysfunction is considered to be a hallmark finding in cirrhotic cardiomyopathy, which is a set of changes in the heart seen in advanced liver disease. We hypothesized that diastolic dysfunction, evidenced by abnormal lateral mitral annular tissue Doppler velocity, would negatively impact survival after liver transplant.

Methods: We performed a retrospective chart review of consecutive adult patients undergoing orthotopic liver transplantation at our institution with available pre-transplant echocardiograms over a ten-year period. The primary outcome was overall post-transplant survival. Cox proportional hazards model was utilized to evaluate the effect of diastolic dysfunction on survival, controlling for covariates previously known to be associated with survival. The benefit of inclusion of tissue Doppler velocity as a marker of diastolic dysfunction in the survival model was assessed with a likelihood ratio test as well Harrell's C-statistic and was compared with other previously reported diastolic parameters.

Results: Over the ten-year study period, 663 patients met inclusion criteria, 135 (20.4%) of whom had abnormal tissue Doppler velocities. Those with abnormal tissue Doppler tended to be slightly older, more often female, and have coronary disease or risk factors such as diabetes, hypertension, or renal disease. Otherwise, the abnormal

and normal groups were well matched in etiology of cirrhosis, model for end-stage liver disease (MELD) scores, and markers of severity of illness including need for vasopressors, dialysis, and mechanical ventilation. After a median follow-up of 36.2 months, abnormal tissue Doppler velocity was shown to have a strong, negative association with survival (hazard ratio [HR] 1.91, $p < 0.0001$) in a model that included race, hepatitis C infection, need for dialysis and mechanical ventilation, recipient age, donor age, and MELD. Other variables that were found to be significant included hepatitis C infection (HR 1.46, $p = 0.01$) and need for dialysis (HR 1.37, $p = 0.049$).

Conclusions: In summary, we find that diastolic dysfunction, as evidenced by abnormal tissue Doppler velocity, is a common abnormality in liver transplant patients and is independently associated with decreased survival. Compared with clinical comorbidities included in the model, it was the most strongly associated with reduced survival, and performed better than other previously published diastolic parameters. Further studies are needed in a multi-center, prospective manner to confirm these findings and clarify the role of diastolic dysfunction in the pre-transplant evaluation of patients.

INTRODUCTION

In the United States there are over 600,000 individuals living with cirrhosis, most commonly due to viral hepatitis, alcohol abuse, and nonalcoholic steatohepatitis (NASH), in addition to a wide variety of other less common etiologies [1]. When cirrhosis progresses to end-stage liver disease (ESLD), the only option to improve long-term survival is liver transplantation (LT) [2], a surgery that can be associated with significant operative time, blood loss [3], metabolic derangements [4], and hemodynamic instability [5]. Patients undergoing LT are increasingly older and have risk factors for cardiac dysfunction including hypertension, obesity, and diabetes mellitus [6], and literature has suggested that patients with proven coronary artery disease (CAD), arrhythmias, or structural heart disease have worse outcomes after liver transplantation [7, 8, 9]. Additionally, it has long been recognized that patients with ESLD often have significant changes in their cardiovascular system attributed to their cirrhosis. These include a drop in systemic vascular resistance associated with an increase in cardiac output [10], ventricular and atria enlargement, increased ventricular wall thickness [11], prolongation of the QT interval [12], impaired systolic function reserve [13], and diastolic dysfunction [14]. These changes, especially the diastolic dysfunction and impaired response to stress, have become the basis of the so-called 'cirrhotic cardiomyopathy.' [15]

Despite the clear intersection of ESLD and cardiovascular disease and the concerns about the impact of heart disease on liver transplant outcomes, the 2012 consensus statement of the American Heart Association and American College of Cardiology Foundation on the evaluation and management of kidney and liver

transplantation candidates has limited recommendations for the pre-operative evaluation of patients undergoing liver transplantation [16]. In this study we sought to better characterize the association between pre-operative diastolic dysfunction and post-LT outcomes, including long-term survival. Diastolic dysfunction has been found to be quite common in this population, with prevalence reported between 26.2% and 43% [17 - 20] depending on patient selection and diastolic criteria used. Diastolic dysfunction prior to LT has been found to be associated with inferior survival [20 - 22] as well as transplant graft rejection [22] and heart failure [21, 22], although at least one study did not find such negative associations [18]. These studies evaluating the effect of diastolic function on survival after liver transplant were generally small [18, 20, 21] with fewer than 200 patients total. These previous studies all rely significantly on transmitral inflow velocities [18, 20 - 22], which have been shown to vary greatly with changes in preload [23, 24]. As patient with cirrhosis frequently become volume overloaded and fluid shifts are common in cirrhosis, these indices may reflect fluctuating volume status as opposed to intrinsic relaxation abnormalities of the ventricle. In contrast, tissue Doppler, specifically the lateral mitral annulus peak velocity, has been shown to be independent to changes in preload [23, 25] and therefore might be a better marker of true diastolic abnormalities as opposed to volume overload alone. We hypothesized that abnormal tissue Doppler velocity (TDV) [26] would correlate with decreased survival after liver transplant, even when controlled for co-morbidities and possible confounders. We also hypothesized that tissue Doppler would provide better discrimination about survival than previously reported measures in this population [18, 20 - 24].

METHODS

Study Design: This was a retrospective chart review of all adult (18 years and older) patients who underwent liver transplant at a large, academic medical center between February 1, 2005 and February 1, 2015. Only patients that had received an organ from a deceased donor after being listed with the United Network for Organ Sharing (UNOS) were included. Patients with a history of heart transplant or who were undergoing a simultaneous heart transplant were excluded, as well as those who had their pre-operative echocardiogram at an outside institution or whose echocardiograms were missing the lateral tissue Doppler velocity or mitral inflow velocities. Patients with conditions that are known to alter tissue Doppler velocities including mitral valve stenosis, repair or replacement, significant mitral annular calcification, or non-sinus heart rhythm were excluded from the study. Patients with systolic dysfunction (ejection fraction < 50% were excluded. If a patient underwent multiple transplants during the time of the study, only the first transplant was included. The institutional review board of the medical center approved the study.

Data Collection: A list of candidate variables for the model for survival after transplant was generated through review of prior literature [17 - 22, 27 - 29] and the Fall 2015 Scientific Registry of Transplant Recipients risk model for three-year survival after deceased donor liver transplantation [30] and consideration of co-morbidities associated with diastolic dysfunction. These variables included recipient age, sex, and race, history of diabetes, coronary artery disease, hypertension, infection with hepatitis C, prior liver

transplant, and hepatic malignancy, model for end-stage liver disease (MELD) score, hospitalization at time of transplant, need for pressors, mechanical ventilation, or dialysis, donor age and sex, donation through cardiac death, cold ischemic time (minutes), and simultaneous kidney transplant. Coronary artery disease included prior myocardial infarction, surgical or percutaneous revascularization, and obstructive or non-obstructive coronary atherosclerosis. Donor, recipient, and surgical variables were obtained via a review of the center's electronic medical record (EMR) system and the center's transplant database. For all patients, the MELD score was calculated without exception points based on published formulas [31] prior to the 2016 update to include sodium in the model.

The echocardiographic variables were obtained via review of transthoracic echocardiogram (TTE) reports and images in the EMR for each patient. The most recent TTE performed closest, but before the transplant, was chosen and no TTEs from outside institutions were utilized. Certified echocardiographers performed the TTEs in the standard views, which included two-dimensional images, pulse wave Doppler, continuous wave Doppler, pulse wave tissue Doppler, and M-mode images. Images were obtained with a Sequoia Acuson ultrasound machine (Siemens Medical Solutions, Malvern, PA, USA) and a Phillips iE33 ultrasound machine (Koninklijke Philips N.V., Amsterdam, The Netherlands). Measurements were made on the machines and separate workstations on commercially available software.

The primary independent echocardiographic variable was the lateral mitral annular velocity on tissue Doppler imaging, (e' , m/s), defined as abnormal when less than 0.10 m/s as suggested by the American Society of Echocardiography (ASE) [25]. Other echocardiographic variables included mitral inflow velocities (E and A, m/s) and deceleration time (ms), left atrial volume index (LAVI, mL/m²), septal mitral annulus tissue Doppler velocity (m/s), and estimated pulmonary artery systolic pressure (mmHg). Ratios of the early to late transmitral inflow velocities (E/A, no units) and of the early transmitral velocity to lateral mitral annular tissue velocity (E/ e' , no units), an estimation of left ventricular filling pressure, were also calculated. Data was complete for most parameters, except for septal tissue Doppler velocity (77% missing), tricuspid regurgitation velocity (19% missing), and LAVI (2% missing).

Data Analysis: Descriptive characteristics for the cohort, as well as comparisons of LT recipients stratified by normal and abnormal TDV, are reported. Categorical variables are reported as percentages and compared with a Fisher's exact test, while non-normally distributed continuous variables are reported as medians with interquartile ranges (IQR) and compared with a Wilcoxon rank-sum test. The primary outcome of interest was the association of abnormal versus normal TDV to post-transplant survival in a covariate-controlled Cox model of post-transplant survival. Survival times were assessed from time of LT to last known time of follow-up as of February 1, 2016, ensuring at least 1 year of follow-up for all included patients. If the patient underwent a re-transplant, survival time was calculated from the time of the first transplant. To generate the model, the cohort was split into normal and abnormal TDV groups, to allow

identification of variables that might be significant within one group and not the other. Within each group Kaplan-Meier curves were constructed for each variable and visually inspected to determine the variables most strongly correlated with survival, an in effort to preserve all alpha error for the final Cox model. To facilitate this, continuous variables were dichotomized based on their median values. Based on the sample size, the top four variables in each group were selected and Cox proportional hazards models were created involving these variables and the TD group variable. Two-way interactions between the TDV variable and other variables were assessed through visual inspection of Kaplan-Meier curves. A full model consisted of all of the identified significant variables, however once the model was made several were found to no longer have significance, and were sequentially removed, recalculating the model each time, until all terms remained significant or near significant ($p < 0.10$). Final hazard rate (HR) ratios of each variable were determined and statistical significance was set at an alpha level of 0.05. All analyses were performed in Stata/IC 14.1 for Mac (64-bit) by StataCorp (College Station, TX, USA).

Validation: The addition of the TDV variable to the model without diastolic function data was assessed via a likelihood ratio (LR) test as they are nested models. Similarly, the addition of other diastolic parameters was tested with an LR test to determine those parameters that had a significant change in the fit of the model. Additionally, the discrimination of the model with and without TDV and the other diastolic parameters was assessed with Harrell's C-statistic. Without an external dataset available for cross validation, and too small of a dataset to split into training and validation datasets,

bootstrapping was utilized to assess for over fitting and correct for optimism in the model, based on a previously published technique [32].

Alternate Model: To see if splitting the model into the normal and abnormal TDV groups to develop the model had an impact, another model was constructed using a backwards stepwise regression using a $p > 0.20$ as the criteria for exclusion from the model. Again, similar validation methods were utilized calculating the LR of including various diastolic parameters and the C-statistics of the different models.

RESULTS

Cohort Characteristics: Of the 1,749 adult liver transplants reviewed for inclusion in the current study between February 2005 and February 2015, 768 were excluded due to their pre-operative echocardiogram being performed at an outside institution; 285 were excluded were non-sinus cardiac rhythm, mitral valve replacement or repair, simultaneous or prior heart transplant, systolic dysfunction, poor echocardiogram quality or missing mitral inflow and tissue Doppler velocity data; and 33 were re-transplants within the dataset (**figure 1**). This resulted in a study population of 663 patients with a median follow-up of 36.2 months: 135 (20.4%) had an abnormal TDV, with 42.2% ($n = 57/135$) mortality during follow-up, while 528 (79.6%) had a normal TDF with 25.2% ($n = 133/528$) mortality during follow-up.

The baseline characteristics of the study population, and comparisons between LT recipients with and without normal TDV, are summarized in **table 1**. Over half (58.8%)

of the transplant recipients were male with a median age of 56 years (IQR 48 to 62 years). Consistent with the demographics of the center's referral area, 37% were Hispanic and 5.4% of the patients were black. Over three-quarters (75.3%) of patients had non-cholestatic cirrhosis as the primary reason for a liver transplant, including etiologies such as alcoholic cirrhosis, autoimmune hepatitis, and the viral hepatitises. Hepatitis C was the most common underlying liver disease (37.6%) at the time of transplant, and 21.2% had a primary liver malignancy, most often hepatocellular carcinoma. Conditions known to be associated with echocardiographic diastolic dysfunction [33] were unevenly distributed between the two groups. Patient with abnormal TDV tended to be older (median 59 versus 54 years) and more often female (54.1% versus 37.9%), and were more likely to have coronary artery disease (15.6% versus 8.0%), diabetes mellitus (45.9% versus 22.4%), and hypertension (38.5% versus 26.7%).

In terms of peri-transplant characteristics, the groups were relatively similar, as depicted in **table 2**. As would be expected with a relatively ill population as evidenced by a median MELD of 33.7 (IQR 24.0 – 39.1), the majority of patients (71.3%) were already hospitalized at the time of transplant. Those with reasons for MELD exception points, such as those with liver malignancies, were much less acutely ill, with a median MELD of 13 (IQR 10 – 23.4) and only a quarter were hospitalized at the time of transplant. Of the entire study group, a significant number (32%) required mechanical ventilation immediately prior to transplant with 19.9% needing the support of pressors. Individuals with abnormal TDV more often needed renal replacement therapy in the week prior to

transplant (53.3% versus 41.9%), but rates of simultaneous liver and kidney transplant were similar between the groups (12.6% versus 10%).

Echocardiographic Characteristics: The echocardiographic characteristics of the study patients are presented in **table 3**. Although only reported in 153 patients (23%), the septal mitral annular TDV was in agreement with the lateral mitral annular TDV in 85% of the cases. Early mitral inflow velocities were lower and late inflow velocities were higher in the abnormal group, resulting in a lower median E/A ratio (0.92 versus 1.3) and a higher proportion of individuals with an E/A ratio < 0.8 (29.6% versus 9.1%, $p < 0.0001$). The median E/e' ratio, an indicator of left ventricular filling pressure, was higher in the abnormal TDV group (11 versus 6.3) and there were significantly more individuals with an E/e' ratio greater than 13 (28.9% versus 0.8%, $p < 0.0001$). Despite these differences, when the information was available, the groups were quite similar in terms of LAVI (median 30.7 ml/m² versus 31 ml/m²), estimated pulmonary artery systolic pressure (median 31mmHg versus 30mmHg), and TR velocity (median 2.5 m/s versus 2.4 m/s). These similarities were preserved across tertiles of MELD scores.

Model Creation: For the abnormal TDV group, recipient age greater, diabetes, need for dialysis, and donor age were the strongest variables (**supplemental figures 1 & 2**). To assess for possible interactions between the above candidate variables and the grouping term, Kaplan-Meier curves for each variable and the TDV term and visually assessed for differences in the variable effect on each group. There appeared to be a possible interaction between diabetes and the group, in which diabetes portended

worse survival in the normal TDV group, but appeared protective in the abnormal TDV group (**supplemental figure 3**). . From these variables and the possible interaction term, Cox proportional hazard models were created, and results are shown in **table 4**.

Outcomes: In the first model including all terms, TDV was highly significant with an HR of 2.15 (95% confidence interval [CI] 1.42 – 3.26, $p < 0.0001$), however there were multiple other terms that did not meet the pre-specified level of significance ($p < 0.05$) or near significance ($p < 0.10$). Diabetes and the associated interaction term were removed, need for dialysis, donor age, and finally black versus non-black race, each time recalculating the Cox model to generate new levels of significance. The final model included hepatitis C, MELD, recipient age, mechanical ventilation, and TDV (HR 1.91, 95% CI 1.38 – 2.63, $p < 0.0001$). The full model with all terms was compared with the reduced model using a likelihood ratio (LR) test, which confirmed that the full model did not have a statistically better fit of the data compared with the reduced model (LR 4.83, $p = 0.305$). In a sub-population of individuals with MELD scores less than 30, TDV remained strongly associated with worse survival (HR 1.72, 95% CI 1.16 – 2.53). Log-log plots of TDV were parallel, which confirms that the proportional hazards assumption needed for the Cox model of this variable was appropriate (supplemental figure 4).

Model Assessment: The models for TDV and other diastolic parameters were assessed using likelihood ratio (LR) test and C-statistics (**table 5**). The C-statistic for the baseline model of infection with hepatitis C, recipient age, MELD, and mechanical ventilation was 0.6239. When TDV was added to the model, the C-statistic improved to

0.6467. The optimism of the models were assessed, and found to be 0.0128 for the model with TDV and 0.0104 for the model without TDV, leaving an optimism-adjusted C-statistic of 0.6338 for the model with TDV and 0.6135 for the model without TDV.

TDV had the highest LR (14.2, $p = 0.0002$), and all terms that did not involvement TDV, including $E/A < 1$, mitral deceleration time $> 200\text{ms}$, and LAVI, did not significantly improvement the fit of the model. Indices of filling pressure, $E/e' > 10$ and $E/e' > 13$, which are ratios that include TDV, had statistically significant LR tests, suggesting they did improve the fit of the baseline model as well. To assess the discriminatory function of the various models, the C-statistics were computed. The model with TDV had the highest value (0.646), although the difference between it and the other models varied from 0.0081 and 0.0228 and is of unclear significance.

The alternate model constructed through stepwise backwards selection returned a similar model to the original method. The terms included were black versus non-black race, infectious with hepatitis C, MELD, recipient age, need for dialysis, and mechanical intubation. Again, TDV and the other diastolic parameters were each added to this model and the resulting models were compared with LR tests and C-statistics with similar results as with the original models (**supplemental table 2**).

DISCUSSION

This study represents one of the largest to examine the impact of echocardiographic abnormalities in liver transplant patients, and is the first to

demonstrate a strong, independent association between tissue Doppler velocity, as a marker of diastolic dysfunction, and survival after orthotopic liver transplantation. Patients with abnormal TDV, defined as lateral $e' < 0.10$ m/s, died 46% faster after liver transplant compared with those with normal TDV, even when controlled for co-morbidities. The difference was seen early after transplant with clear separation of the survival curves within six months with a continued separation throughout all of follow-up.

Diastolic dysfunction is a relatively common condition in patients with advanced cirrhosis, and the hallmark of the so-called cirrhotic cardiomyopathy. We found 20.4% of individuals with abnormal TDV, our chosen marker of diastolic dysfunction. This prevalence is somewhat lower than previously published rates of diastolic dysfunction which ranged from 15% to 43% with most studies demonstrating greater than 25%, depending on the definition used [17 – 22]. The only other study to solely use TDV reported a prevalence of 38%, but this was a much smaller study of healthier patients and did not assess patients going to transplant [17]. Using the definitions of other studies, including $E/A < 1$, deceleration time less than 200ms, $E/e' > 13$, and $LAVI \geq 34$ ml/m², our population still had lower than reported prevalence. This may relate to differences in the study populations. While most other studies did not report cardiac co-morbidities, our patients less often had hypertension (29.1%) or diabetes (27.2%) compared to studies where 42-47% of patients had diabetes and 48-60% of patients had hypertension [21, 22]. Our patients also had a higher acuity compared to other studies, with over 70% of patients hospitalized at the time of transplant and a median laboratory MELD of nearly 33.7 compared with MELDs reported between 13 and 22 in other studies [17 – 22]. While studies have demonstrated a link between higher MELD

and diastolic dysfunction [34] these associations are cross sectional, and do not account for how long each patient had cirrhosis.

As expected, patients with abnormal TDV were more likely to have other abnormal diastolic parameters. Those with abnormal tissue Doppler had lower early peak mitral inflow velocities and higher late peak velocities, resulting in a lower E/A ratio and a higher E/e' ratio, suggesting increased filling pressures. *Raevens et al* [18] found similar associations in diastolic parameters in cirrhotic patients as well. Interestingly, pulmonary artery systolic pressure, tricuspid regurgitation velocity, and left atrial volume index were similar in the groups with normal and abnormal tissue Doppler. Over time, impaired left ventricular filling gives rise to elevated pressures [35] that will cause atrial dilation and this combined with increased fluid retention generally will cause an increase in pulmonary pressures. However, atrial size and pulmonary pressures are influenced by multiple factors outside of myocardial relaxation, including renal dysfunction and systemic hemodynamics [36, 37]. Cirrhosis is a high-output state and increased cardiac flows over time will result in atrial dilation [37]. Our patient population had advanced cirrhosis, evidenced by their need for a liver transplant and a high laboratory MELD, which may explain the enlarged atria seen in the entire cohort and the lack of a difference in the groups based solely on the TDV grouping. Additionally, as would be expected with advanced cirrhosis, renal failure was highly prevalent, with 44.2% requiring dialysis, and these individuals may be more likely to be intravascularly overloaded causing the elevated pulmonary pressures.

Due to the limited size of patient cohort, we could not include all possible comorbidities that have been reported to be associated with post liver transplant survival.

Instead, to assess the association of TDV on survival, we first developed a model for survival after liver transplant. Previous models for post transplant survival were determined in patient populations that may have varied significantly from our cohort. Therefore, co-morbidities found to significantly influence survival in prior literature may not have a similar impact in our patient population, and thus we constructed a survival model specific for our patient population using visual assessment of each candidate variable. Many candidate variables did not demonstrate a significant association with survival, including the terms associated with diastolic dysfunction in our cohort such as recipient sex, hypertension, and coronary artery disease. Previous studies have also found sex [28, 38] and hypertension [39] not to be associated with survival after liver transplant. Coronary artery disease has been noted in some studies [40] to be associated with a poor outcome after transplant, but in our study the unadjusted hazard ratio was 1.34 (95% CI 0.83 – 2.15). This may be in part to a looser definition of coronary artery disease in this study, which did not require prior myocardial infarction or revascularization. Diabetes, which has been shown in some studies and registries [31, 39] to be associated with post liver transplant survival, did appear associated with survival in our cohort. It was included in the original model, but with the addition of other variables, diabetes was no longer a significant variable in the model and was removed. Our final model included, recipient age, MELD, infection with hepatitis C, and mechanical ventilation, all of which have been found to be negatively associated with survival in prior literature [30, 41, 42] in addition to TDV. Within this model, abnormal TDV was found to have the strongest influence on survival of all terms in the model.

Although the pathophysiology of diastolic dysfunction in cirrhosis is not fully characterized, numerous pathways and factors have been implicated, including myocyte hypertrophy [43], beta-receptor down-regulation [44], and dysfunction of K⁺, Ca⁺⁺ [45] and other signaling channels and pathways. These abnormalities are compounded by significant systemic vasodilation, and while intravascular volume is increased, effective central hypovolemia results in activation of the renin-angiotensin-aldosterone (RAA) system as well as increased sympathetic tone, resulting in an increased resting heart rate, high-output circulatory state, abnormal sodium and fluid retention, and renal dysfunction [46]. This is evidenced by the high rates of dialysis in the study population (44.2%) with disproportionately low rate of simultaneous renal transplant (10.6%) as LT corrects these abnormalities restoring normal renal perfusion. In our study, patients with abnormal TDV had a higher rate of dialysis (53.3% versus 41.9%), which may be in part due to the impaired renal response to volume overload in patients with diastolic dysfunction [47], and thus a greater need to use renal replacement therapies to more aggressively control volume status prior to transplant.

This is detrimental for individuals with abnormal myocardial relaxation as they have an impaired ability to handle volume expansion, especially in the setting of tachycardia as their ventricles need more time to fill completely. The result can be worsening fluid retention, pulmonary edema, and a reduced cardiac output. Unfortunately, in the current study, we do not have information regarding the cause of death or complications to try to determine mechanisms between abnormal diastolic function and the poor outcomes in our patient cohort.

While the main objective of the study was to characterize the association of abnormal tissue Doppler and survival, we also sought to assess the performance of the model and the information gained from including the TDV variable. There are many ways to assess the utility of a model based, but essentially it is an issue of whether a model reliably predicts what it is supposed to predict. The optimism-corrected c-statistic (concordance) of the model improved from 0.6138 without a diastolic parameter to 0.6338 with the additional of TDV. While the model's c-statistic is somewhat lower than other models for survival [28, 29], our models were constructed on long-term survival data, and the accurate prediction of survival times over longer periods of survival may be more difficult as post-transplant conditions and variables begin to play a larger role in survival compared with the data available immediately prior to transplant. In terms of comparing diastolic parameters, LR testing demonstrating that diastolic indices other than TDV or those that included TDV ($E/e' > 10$ and $E/e' > 13$) did not improve the fit of the model. While TDV did have a higher c-statistic than the estimates of filling pressures, $E/e' > 10$ and $E/e' > 13$, implying better discriminatory function of TDV-based model, it is not clear that the difference is meaningful. This may be because the filling pressure estimates inherently include TDV as part of them. Regardless, TDV appears to be strongly associated with worsened survival and perform better than diastolic indices that do not include TDV.

Limitations: There are several limitations to our study that merit discussion. While this is one of the largest in the literature, 44% of the patients screened for inclusion were excluded as their echocardiogram occurred at an outside institution. This was

necessary as these studies were not available for review and not all centers measure and report the needed values. The patients excluded tended to be less ill, as evidenced by lower MELD scores, not being hospitalized at the time of transplant, and less need for vasoactive medications, mechanical intubation, and dialysis (**supplemental table 1**). While this may explain the lower median survival of patients in the study than otherwise might be expected in an all-inclusive study, it should not negate the impact of abnormal TD in this population. Whether such a profound difference in survival based on TD might be seen in healthier population needs further exploration. Additionally, not all patients had their echocardiogram done at the same time interval prior to transplant, with a median time between echocardiogram and transplant of 21 days, without a significant difference between groups. While this does introduce a level of uncertainty in the data, it is reflective of actual practice, and it is unclear that this will bias the results. With a limited patient cohort, not all variables that have previously associated with post transplant survival could be included in the model. This raises the possibility that with enough other clinical variables, the diastolic variable would have less impact in the model's accuracy. Finally, with an external dataset or a larger single-center dataset, different validation techniques such as external validation or splitting the dataset into training and validation cohorts could have been performed.

Conclusion: In summary, we find that diastolic dysfunction, as evidenced by lateral mitral tissue Doppler velocity less than 0.10m/s, is a common abnormality in liver transplant patients and is independently associated with decreased survival. Compared with clinical comorbidities included in the model, it was the most strongly associated

with reduced survival, and performed better than other previously published diastolic parameters that do not consider tissue Doppler velocity. Further studies are needed in a multi-center, prospective manner to confirm these findings and clarify the role of diastolic dysfunction in the pre-transplant evaluation of patients.

FIGURES AND TABLES

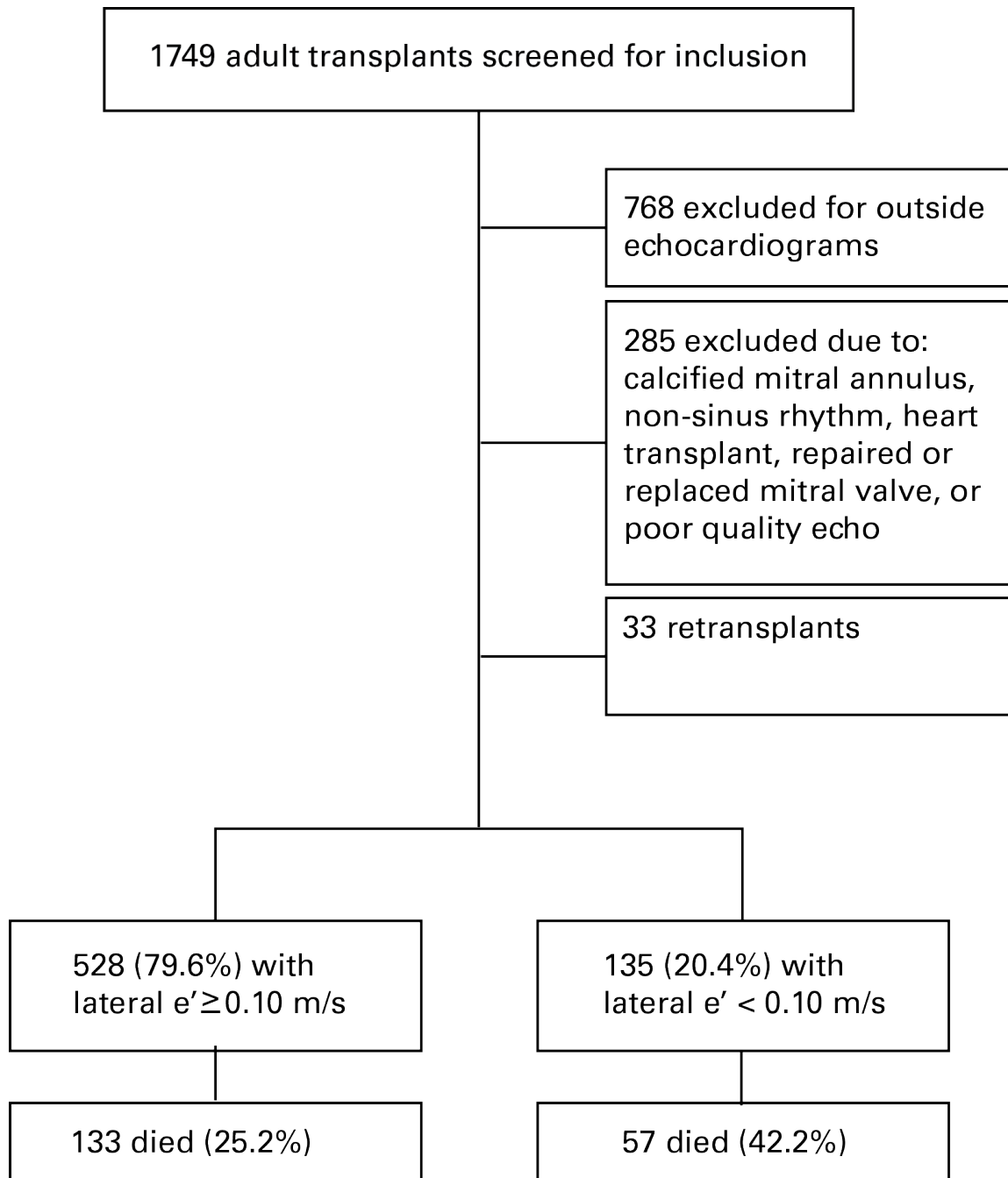


Figure 1: Patient selection diagram

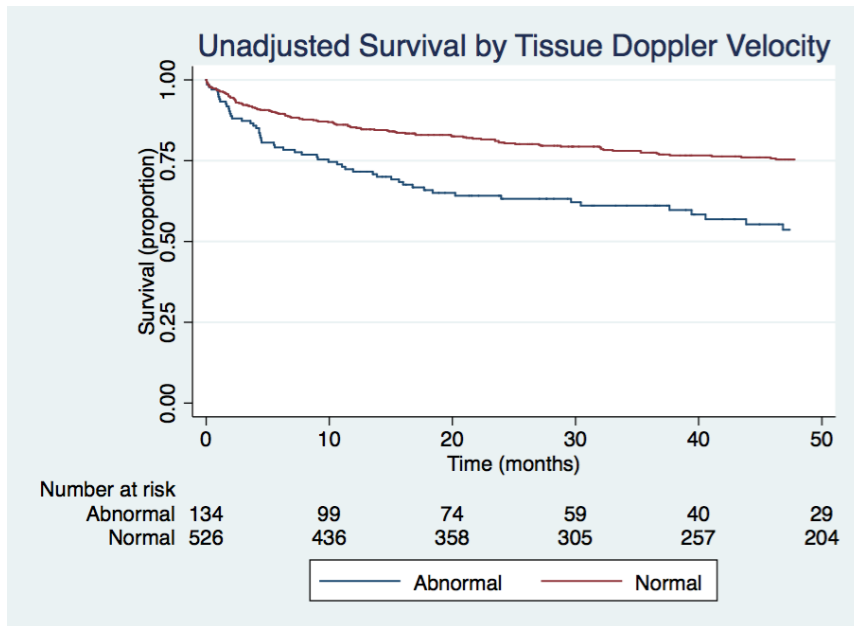


Figure 2: Shown above is the unadjusted Kaplan-Meier curve for survival stratified by whether or not a patient's tissue Doppler velocity was less than 0.10 m/s (abnormal) or greater than or equal to 0.10m/s (normal). Number at risk shown below, stratified by group.

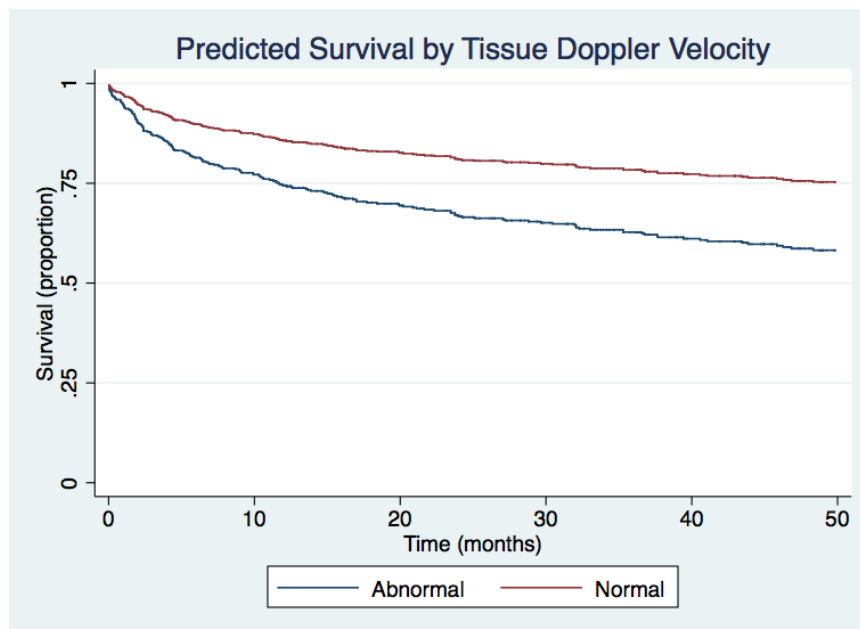


Figure 3: Shown above are the predicted survival curves for individuals with tissue Doppler velocity less than 0.10 m/s (abnormal) or greater than or equal to 0.10 m/s (normal). The baseline survival function was estimated from the Cox model, and other variables were set to mean values for the entire study population.

	Total Cohort	Normal TDV	Abnormal TDV	p-value
Age (years)	56 (48 - 62)	54 (47 - 61)	59 (54 - 64)	<0.0001
Age > 65 years	11.9%	10.6%	17.0%	0.04
Male	58.8%	62.1%	45.9%	0.001
Race				0.192
White	45.1%	45.1%	45.2%	
Black	5.4%	5.1%	6.7%	
Hispanic	37.0%	38.1%	32.6%	
Asian	11.3%	10.2%	15.6%	
Other	1.2%	1.5%	0.0%	
CAD	9.5%	8.0%	15.6%	0.007
Diabetes	27.2%	22.4%	45.9%	<0.001
Hypertension	29.1%	26.7%	38.5%	0.007
Hepatitis C	37.9%	36.7%	42.2%	0.241
Liver Malignancy	21.3%	20.5%	24.4%	0.312
Prior Transplant	6.2%	5.9%	7.4%	0.508
Cirrhosis Etiology				0.831
Non-cholestatic	75.3%	74.8%	77.0%	
Cholestatic	5.3%	5.5%	4.4%	
Other	19.5%	19.7%	18.5%	

Table 1: CAD = coronary artery disease, TDV = tissue Doppler velocity

	Total Cohort	Normal TDV	Abnormal TDV	p-value
Lab MELD	33.7 (24.0 - 39.1)	33.5 (23.9 - 39.1)	33.9 (25.0 - 38.7)	0.719
Hospitalized at Transplant	71.30%	71.40%	71.00%	0.947
Requiring Dialysis	44.2%	41.9%	53.3%	0.017
Mechanical Ventilation	32.0%	32.6%	29.6%	0.512
Requiring Vasopressors	19.9%	18.9%	23.7%	0.216
Donation via Cardiac Death	3.9%	3.8%	4.4%	0.726
Male Donor	63.8%	64.8%	60.0%	0.303
Donor Age (years)	39 (24 - 52)	38 (24 - 51)	40 (26 - 54)	0.276
Cold Ischemic Time (hours)	6.8 (5.4 - 8.4)	6.8 (5.4 - 8.4)	6.8 (5.4 - 8.4)	0.668
Simultaneous Kidney Transplant	10.6%	10.0%	12.6%	0.389

Table 2: Peri-transplant and transplant characteristics of the cohort, MELD = model for end-stage liver disease, Lab MELD is based only on the lab data, excluding any exception points, TDV = tissue Doppler velocity

	Normal TDV	Abnormal TDV	p-value
Lateral TDV (m/s)	0.14 (0.12 - 0.17)	0.08 (0.07 - 0.09)	<0.0001
Septal TDV (m/s)*	0.10 (0.08 - 0.12)	0.07 (0.05 - 0.08)	<0.0001
Early mitral inflow (E, m/s)	0.9 (0.8 - 1.1)	0.8 (0.6 - 1)	0.0003
Late mitral inflow (A, m/s)	0.7 (0.6 - 0.9)	0.8 (0.6 - 0.9)	0.0165
Mitral valve deceleration time	221 (190 - 264)	246 (205 - 283)	0.001
E/A ratio	1.3 (1 - 1.5)	0.92 (0.75 - 1.3)	<0.0001
E/e' ratio	6.3 (5 - 7.9)	11 (7.6 - 13.8)	<0.0001
TR velocity (m/s)+	2.5 (2.2 - 2.7)	2.4 (2.2 - 2.7)	0.92
Right ventricular systolic pressure (mmHg)+	31 (24 - 37)	30 (24 - 37)	0.644
Left atrial volume index (ml/m2)^	30.7 (24.7 - 40.3)	31.0 (23.5 - 43.5)	0.496

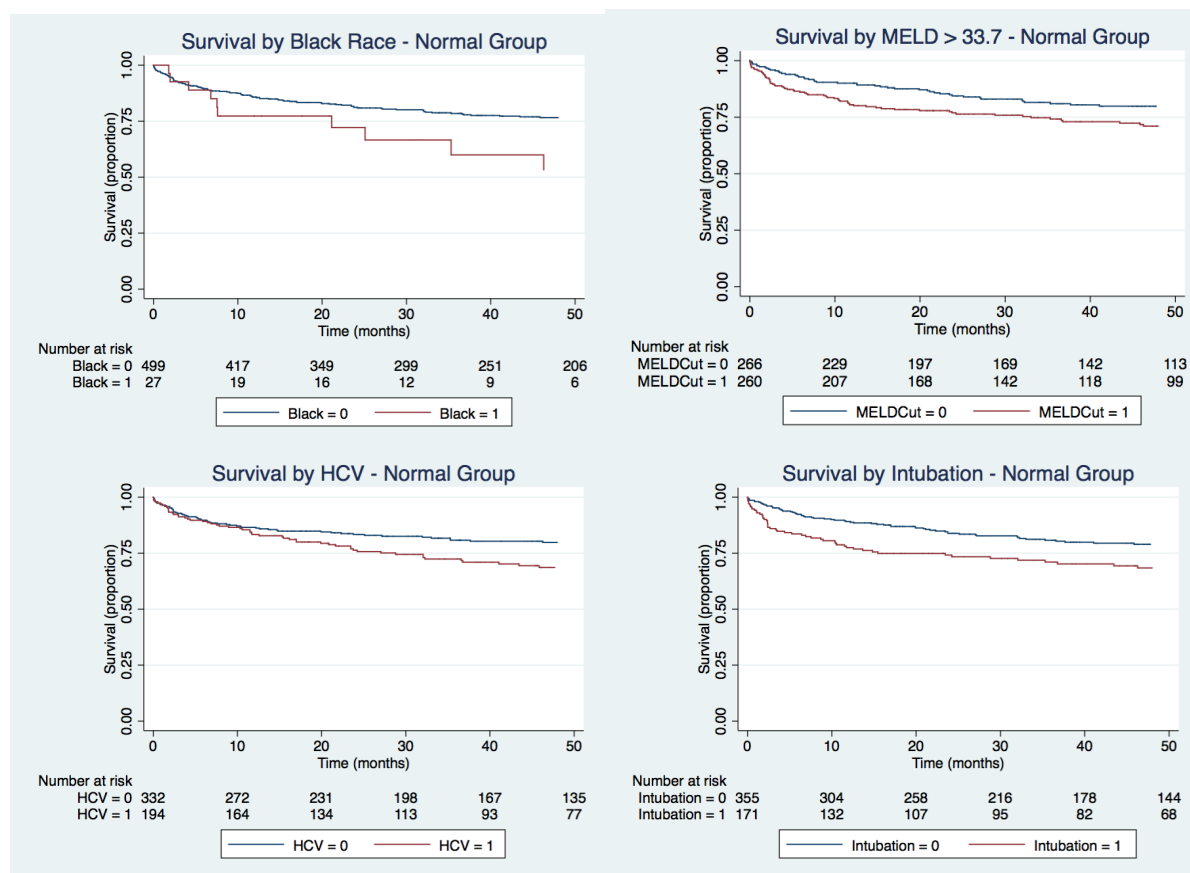
Table 3: Echocardiographic Characteristics, TR = tricuspid regurgitation, TDV = tissue Doppler velocity

	Full Model		Reduced Model	
	HR	p-value	HR	p-value
Black v. non-black Race	1.58 (0.94 - 2.65)	0.085	-	-
Hepatitis C	1.37 (1.02 - 1.83)	0.039	1.41 (1.06 - 1.89)	0.02
Requiring dialysis	1.21 (0.84 - 1.75)	0.301	-	-
Diabetes	1.23 (0.83 - 1.82)	0.304	-	-
MELD (per 10 points)	1.11 (0.93 - 1.35)	0.243	1.16 (1.01 - 1.36)	0.042
Donor Age (per 10 years)	1.06 (0.96 - 1.16)	0.245	-	-
Recipient Age (per 10 years)	1.17 (1.01 - 1.37)	0.038	1.21 (1.04 - 1.40)	0.013
Mechanical ventilation	1.33 (0.96 - 1.85)	0.082	1.36 (0.99 - 1.88)	0.054
Tissue Doppler velocity (TDV)	2.15 (1.42 - 3.26)	<0.0001	1.91 (1.38 - 2.63)	<0.0001
TDV by diabetes interaction	0.64 (0.33 - 1.25)	0.196	-	-

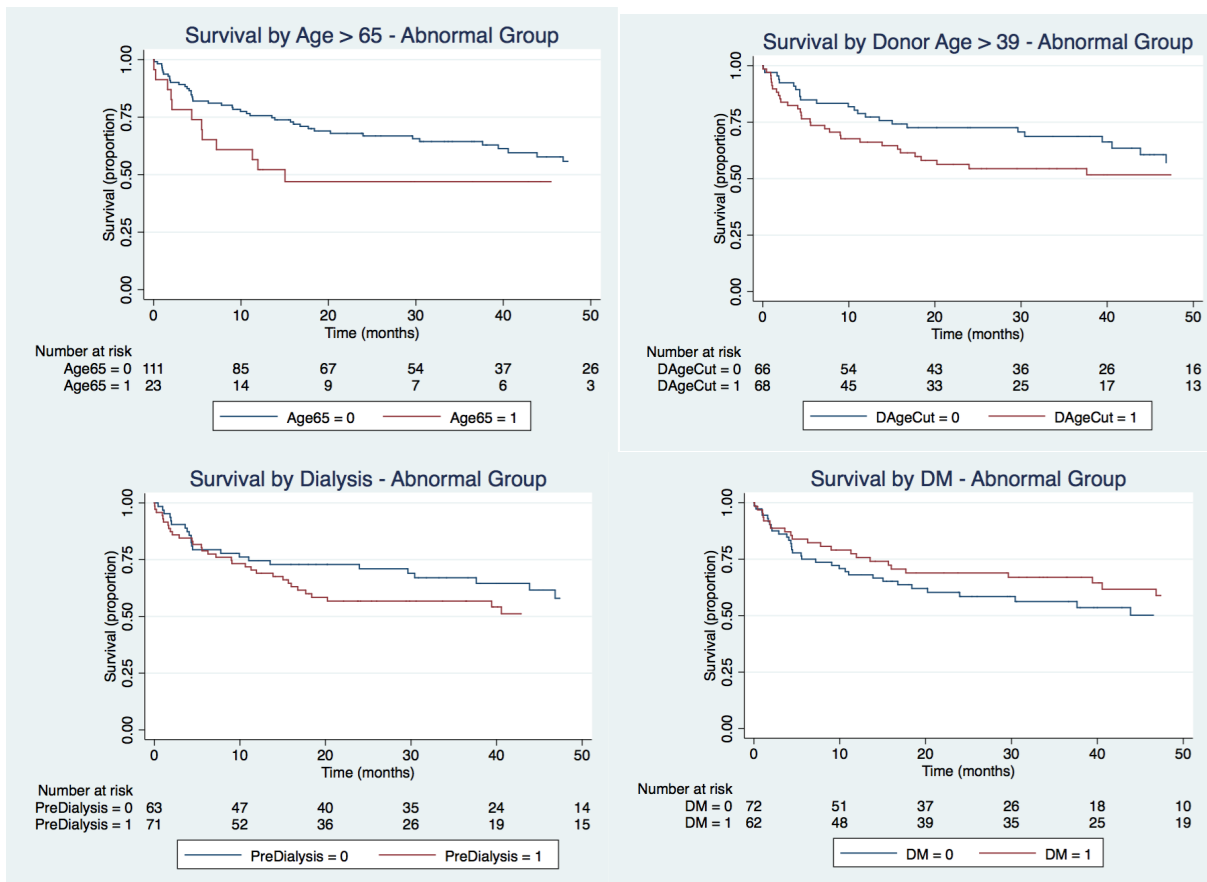
Table 4: The Cox models for survival, including the full model and the reduced model for terms p < 0.10. MELD = model for end-stage liver disease

Table 5. Comparing Diastolic Markers			
	Likelihood-ratio (LR)	p-value	Harrell's C
Tissue Doppler velocity (TDV)	14.2	0.0002	0.6467
E/e' > 10	5.38	0.0204	0.6386
E/e' > 13	4.72	0.0298	0.6333
Mitral valve deceleration time > 200ms	2.52	0.107	0.6311
E/A < 1	0.95	0.3303	0.6251
LAVI > 34 ml/m2	0.32	0.5717	0.624
LAVI > 40 ml/m2	0.01	0.9391	0.6239

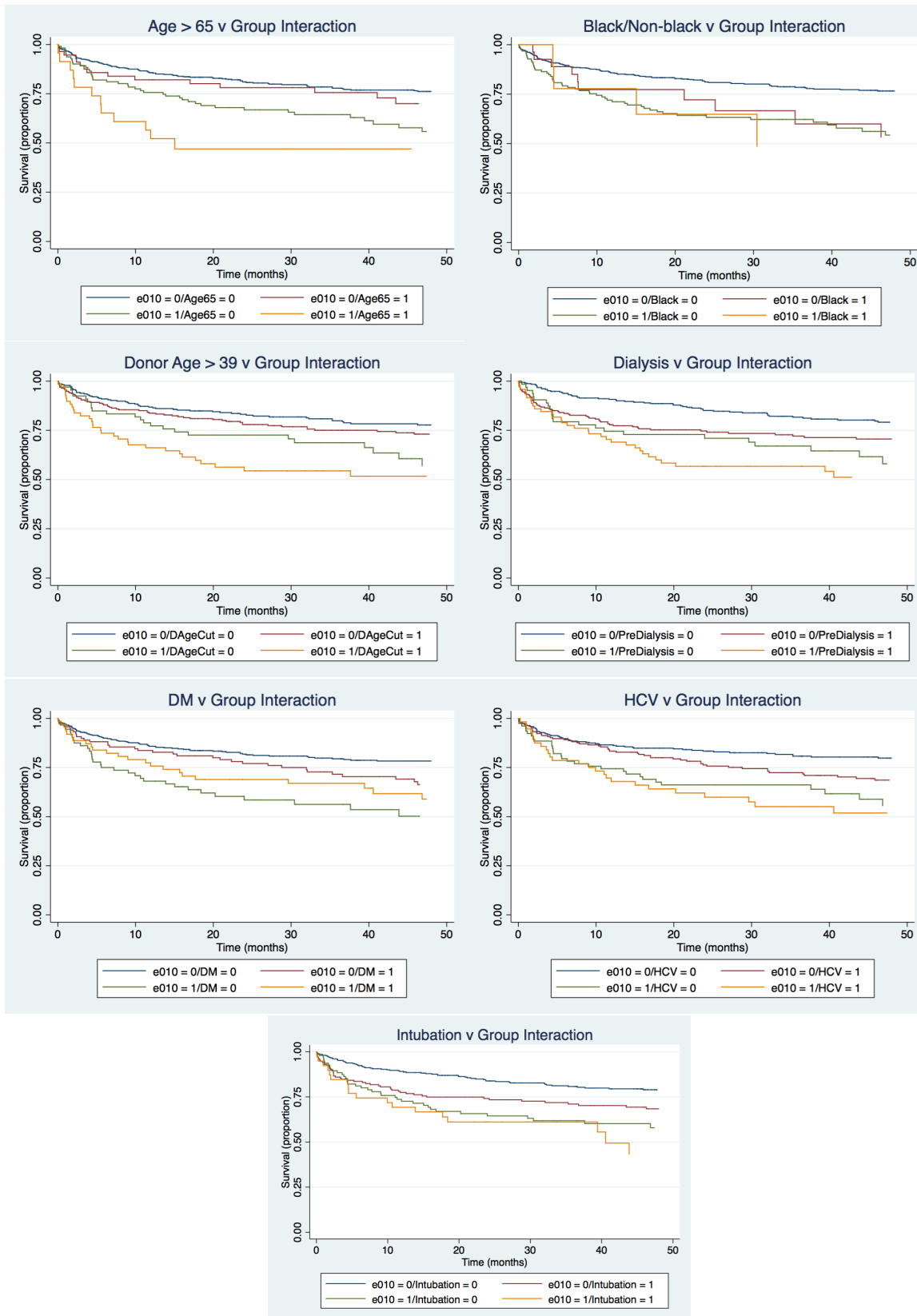
Table 5: E = early mitral inflow peak velocity, A = late mitral inflow peak velocity, LAVI = left atrial volume index



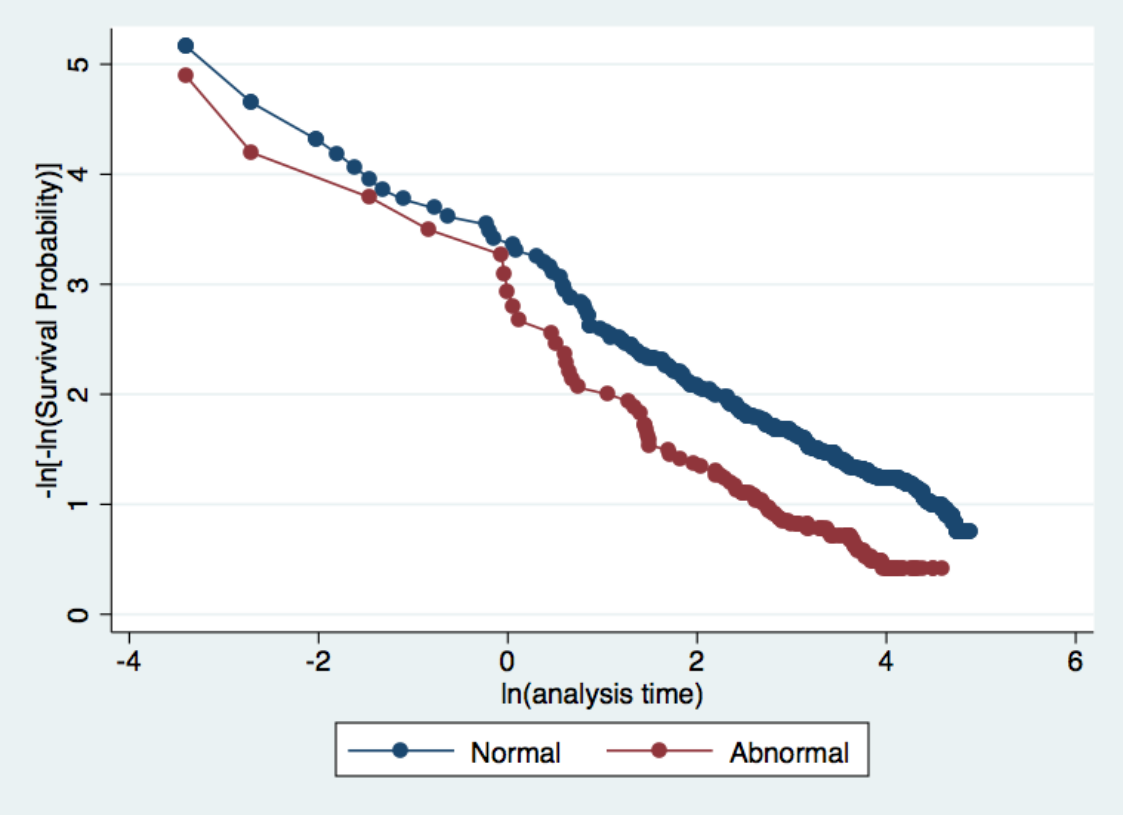
Supplemental Figure 1: Kaplan-Meier survival curves for the normal tissue Doppler velocity group for black versus non-black race, hepatitis C infection, mechanical ventilation, and MELD > 33.7



Supplemental Figure 2: Kaplan-Meier survival curves for the abnormal tissue Doppler velocity group for age greater than 65 years, donor age greater than 39 years, need for dialysis, and diabetes



Supplemental Figure 3: Kaplan-Meier curves for each variable and grouping term to assess for possible interactions.



Supplemental Figure 4: Log-log plots by tissue Doppler velocity (TDV) to assess whether the proportional hazards assumption for the Cox model was appropriate.

Table S1. Cohort Bias		
	Included Patients	Excluded Patients
Age (years)	56 (48 - 62)	56 (50 - 61)
Male	58.8%	67.9%
CAD	9.5%	6.0%
Diabetes	27.2%	24.3%
Hypertension	29.1%	28.5%
Prior Transplant	6.2%	4.6%
Lab MELD	33.7 (24.0 - 39.1)	25.6 (14 - 36)
Hospitalized at Transplant	71.30%	38.4%
Requiring Dialysis	44.2%	22.7%
Mechanical Ventilation	32.0%	14.0%
Requiring Vasopressors	19.9%	7.5%
Donation via Cardiac Death	3.9%	5.2%
Male Donor	63.8%	62.0%
Donor Age (years)	39 (24 - 52)	41 (25 - 53)
Cold Ischemic Time (hours)	6.8 (5.4 - 8.4)	6.7 (4.9 - 8.5)
Simultaneous Kidney Transplant	10.6%	5.7%

Supplemental Table 1: Comparing characteristics of the included patients and those excluded during patient selection.

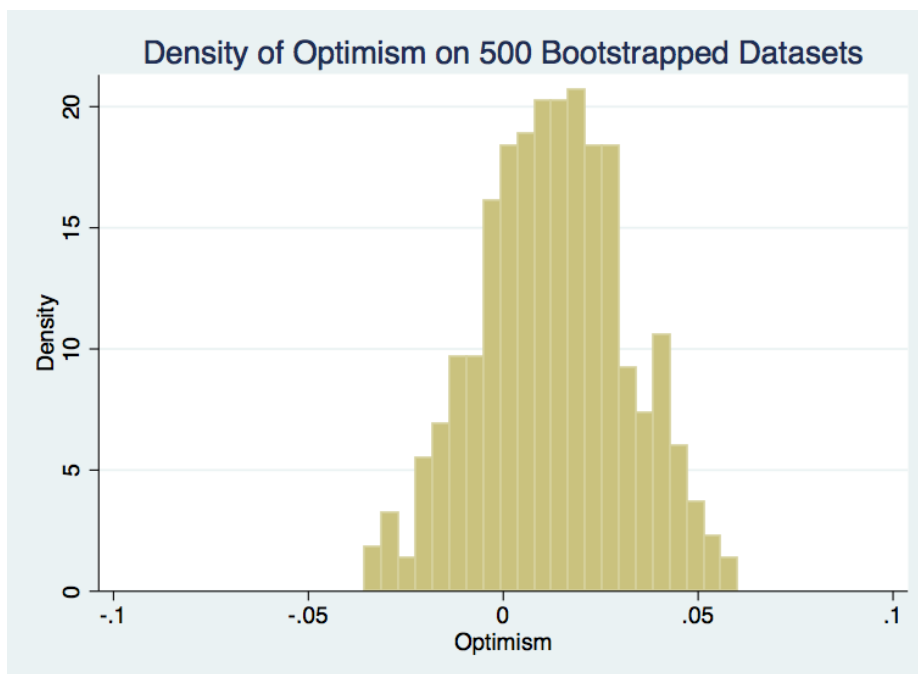
Table S2. Alternate Model Comparisons			
	Likelihood-ratio (LR)	p-value	Harrell's C
Tissue Doppler velocity (TDV)	13.46	0.0002	0.6528
E/e' > 10	6.45	0.0111	0.6452
E/e' > 13	5.23	0.0222	0.6395
Mitral valve deceleration time > 200ms	3.53	0.0602	0.6381
E/A < 1	0.78	0.3786	0.6317
LAVI > 34 ml/m ²	0.24	0.6242	0.6306
LAVI > 40 ml/m ²	0.01	0.9386	0.6296

Supplemental Table 2: Comparing the performance of diastolic parameters in an alternate model constructed through backwards stepwise regression with a p < 0.20 cut-off for inclusion in the model resulting in model terms: recipient age, hepatitis C, need for dialysis, black versus non-black race, mechanical intubation, MELD.

CHAPTER 2: STATISTICAL APPENDIX

Optimism correction: A secondary aim of the study was to assess how the addition of information regarding diastolic function, in this case tissue Doppler velocity, improved the model's function, and for this, Harrell's (concordance) statistic was chosen as a means of measuring the model's discrimination. Since survival models are generally do not predict exact survival times for each patients, models are assessed on discriminating individuals who have a higher risk for reaching an event (in this case death) from those with a lower risk. Harrell's C-statistic is calculated by assessing all pairs of events in which one subject survives another, and assessing the percentage of times in which the model gave a higher hazard rate to the one that died first, with ties being divided by two. It varies from 0.5 to 1.0 in which higher values signify better discriminatory function, and as stated in the manuscript, the C-statistic improved from 0.6239 to 0.6467. Unfortunately, these values include optimism, which is the over-fitting of models to the data from which they were derived, giving an inflated sense of discriminatory function. Under the best of conditions, including very large datasets and multiple datasets from different sites, models can be derived in one dataset and then tested on an external dataset or a single, large dataset can be split randomly into training and testing datasets. However, in this case, no external data was available and the dataset was too small to split. An alternative, as described by Harrell [29] is to use bootstrapping, or sampling with replacement on the original dataset in order to estimate the optimism and therefore correct the originally derived C-statistic.

Initially the “apparent” C-statistic (Capp) was calculated using the full, original dataset using a Cox model with the variables: hepatitis C infection, MELD, recipient age, need for mechanical ventilation, and TDV, giving a value of 0.6467. A new dataset of the same size of the original was generated via sampling the original with replacement. From this new dataset, a new Cox model was fit for the same variables, giving new coefficients. The “bootstrap” C-statistic (Cboot) was calculated using the new model on the new dataset. Then discrimination of this new model on the original data or the “original” C-statistic (Corig) was calculated. The difference of Corig and Cboot was to the optimism of the bootstrapped sample. This process from generating the bootstrapped sample through calculated the optimism of the sample was repeated hundreds of times and the average of the values of optimism was calculated. In our dataset, this was found to be 0.0142, giving an optimism-corrected C-statistic of $0.6467 - 0.0128 = 0.6387$.



Appendix Figure 1: A density plot of the optimism of the model calculated on 500 bootstrap datasets, mean 0.01287, standard deviation 0.0187

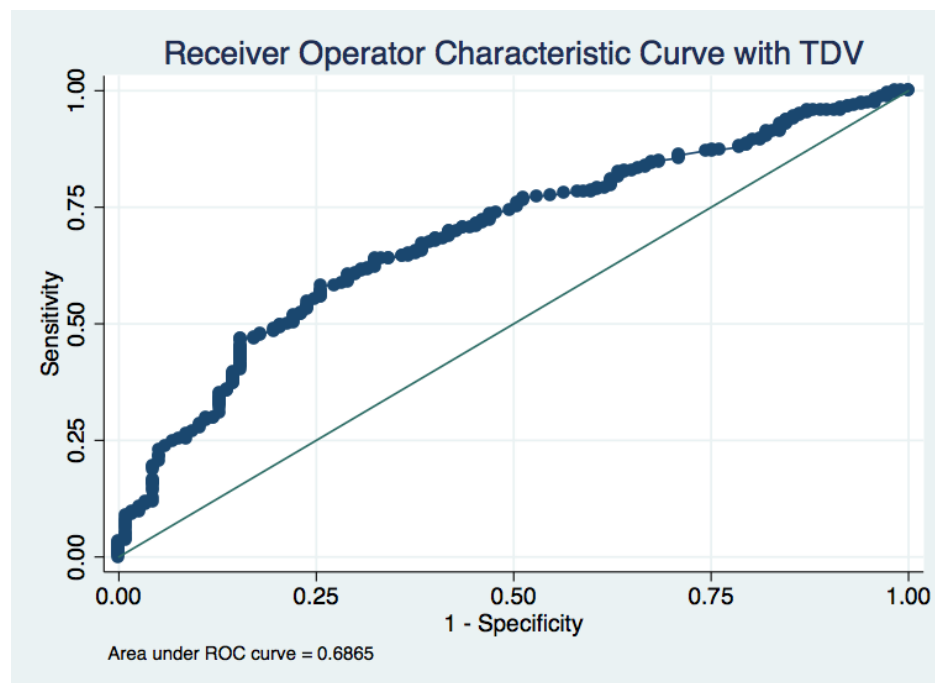
One Year Survival Model: The primary focus was on the association of tissue Doppler and survival, and so the Cox model was developed for long-term survival. In addition to understanding factors that influence survival after liver transplantation, certain milestones in survival are considered important, one of which is survival to one year after transplant. Failure to reach that mark may suggest poor patient selection and resource utilization. This was investigated using a logistic regression model in which survival to one year was the outcome. Given that this shorter-term outcome may be influenced differently by the pre-transplant variables, a backwards stepwise selection was done using a cut-off of $p > 0.15$ for exclusion from the model. All candidate variables were included in the selection process, and the resulting model included the terms of mechanical ventilation, hospitalized at transplant, recipient age, need for dialysis, and TDV.

One Year Survival Model		
	Odds Ratio (OR)	p-value
Need for dialysis	0.59 (0.37 - 0.94)	0.027
Tissue Doppler velocity (TDV)	0.52 (0.32 - 0.82)	0.006
Recipient age (per 10 years)	0.77 (0.63 - 0.96)	0.017
Mechanical ventilation	0.65 (0.41 - 1.03)	0.065
Hospitalized at transplant	0.65 (0.36 - 1.15)	0.135

Appendix Table 1: Odds ratios and associated p-values of a logistic regression model for survival to at least one year after transplant

Whereas the long-term survival model was a Cox proportional hazards model and the discriminatory function of the model was assessed with Harrell's C-statistic, the discriminatory function of this logistic regression model can be assessed with a receiver operator characteristic curve. For each patient the model can be used to create a

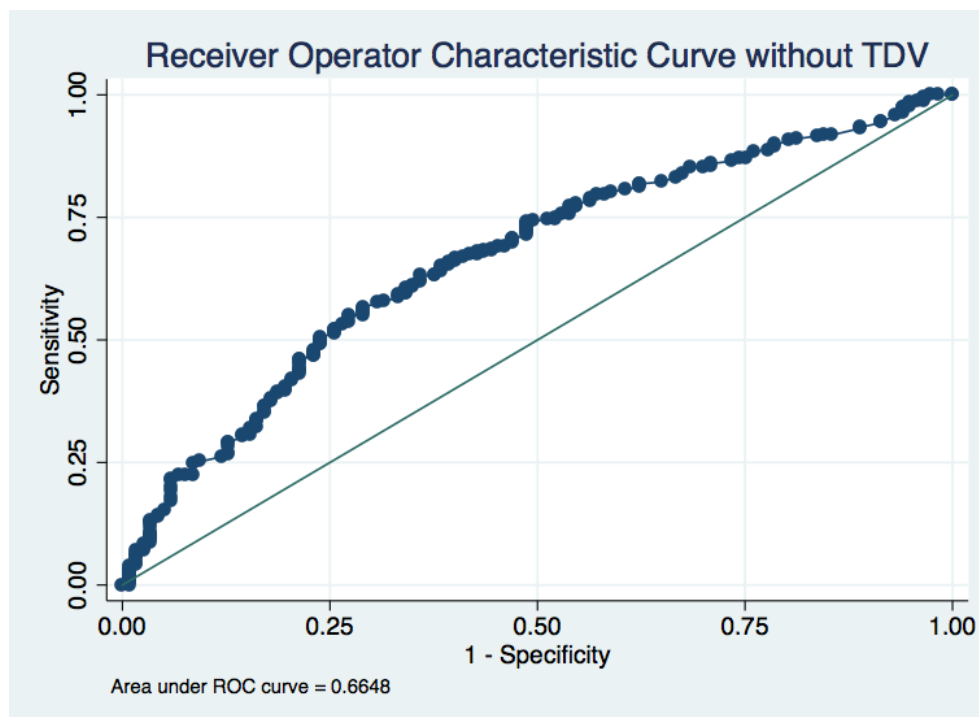
probability of the outcome, survival through the first year after transplant. A curve can be generated by selecting and varying a cut-off for the probability at which a patient will be classified as expected to be alive at the end of a year and comparing it to the observed outcomes using a standard two by two table and then plotting sensitivity against 1 – specificity, a receiver operator characteristic (ROC) curve. The area under the curve (AUC) can be determined and this is the discriminatory ability, or c-statistic, of the model and like the long-term survival model, it varies from 0.5 to 1.



Appendix Figure 2: Receiver operator curve (ROC) of the logistic regression model of one-year survival including tissue Doppler data

In this model, the AUC was 0.6865, better than the 0.6455 achieved with the long-term survival model. This is to be expected as survival in the first year after liver transplant is more likely to be explained by pre-transplant characteristics and the overall severity of illness immediately prior to transplant, compared with survival up to ten years after transplant. Over a greater follow-up, it is more likely that survival becomes influenced by unmeasured variables, changes in pre-transplant variables, or chance events. Like

with the long-term survival model, then a base model without the tissue Doppler variable was created and the ROC curve formed.



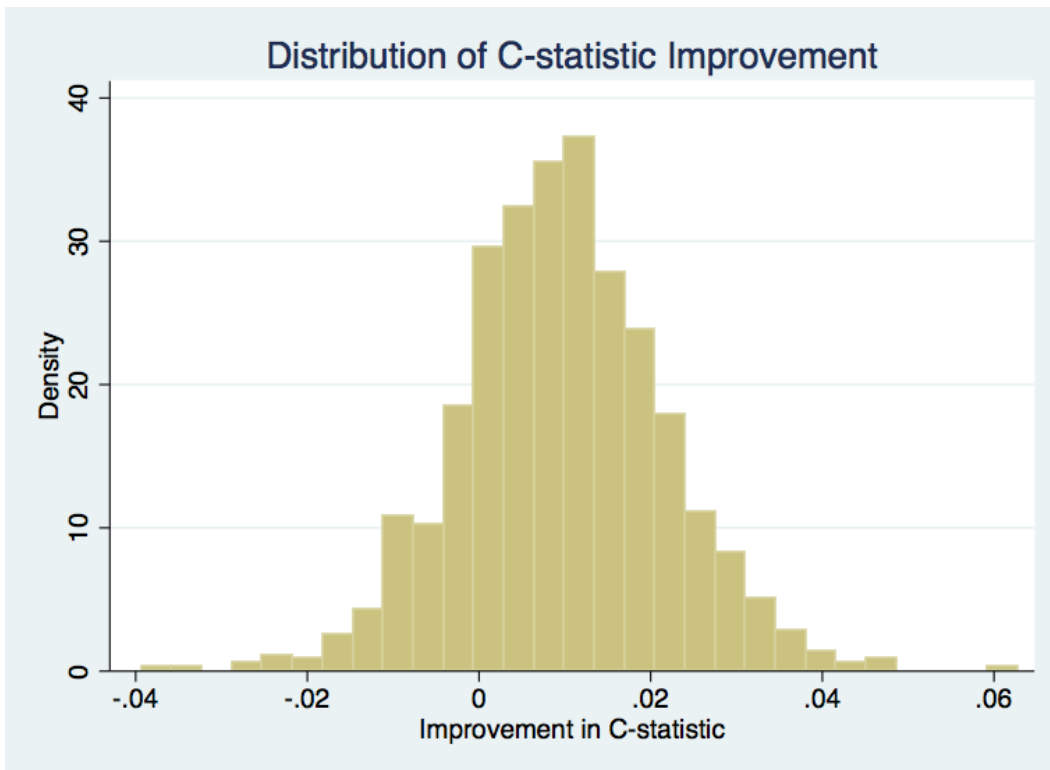
Appendix Figure 3: Receiver operator curve (ROC) of the logistic regression model of one-year survival excluding tissue Doppler data

The base model had an AUC of 0.6648, suggesting worse discriminatory function compared with the full model that includes the tissue Doppler variable. As the two models were nested, a likelihood ratio (LR) test was used to assess the goodness-of-fit of the models, and the full model was found to fit the data statistically better than the base model (LR = 7.4, p-value = 0.0065). This suggests that diastolic dysfunction, represented by tissue Doppler velocity may play a role in assessing probability of one-year survival after liver transplant.

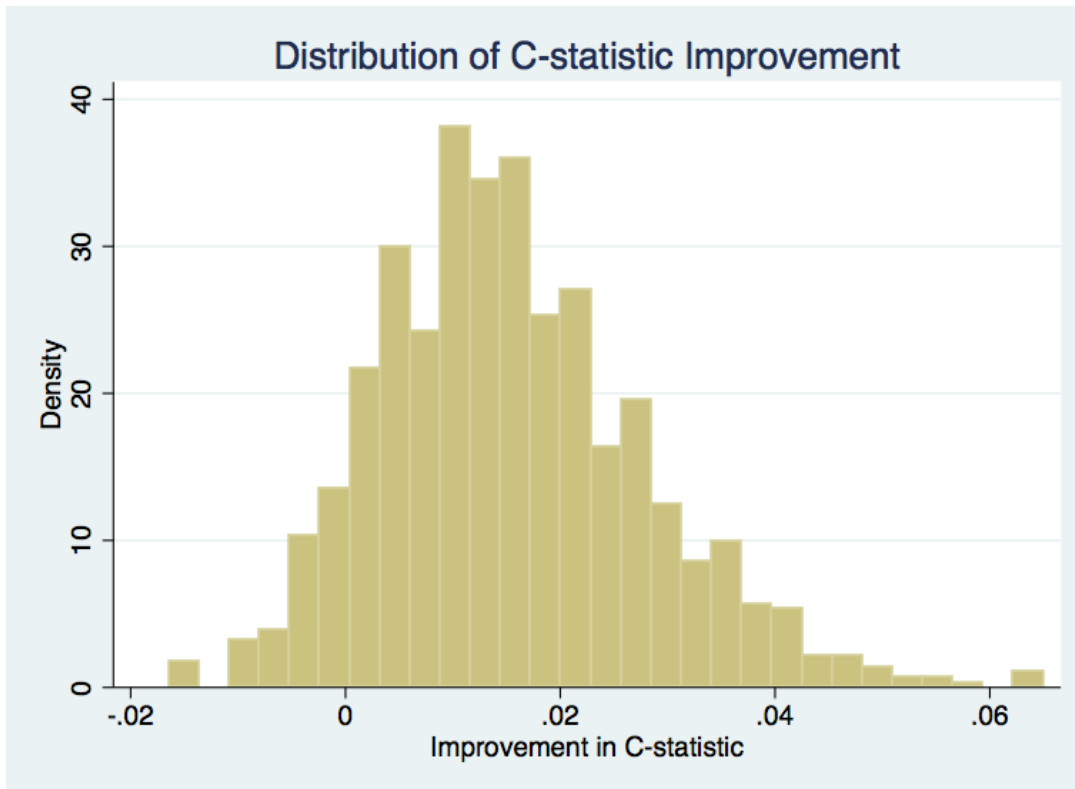
Diastolic Parameter Comparison: Multiple studies have suggested that diastolic dysfunction has a negative association with survival after liver transplantation. Given the complex nature of diastolic function, however, various parameters have been

proposed in prior literature to categorize liver transplant candidates as having normal or abnormal diastolic function. One of the secondary aims of the study was to assess whether tissue Doppler alone was better than other previously described parameters in assessing survival after transplant. Given the correlation between different parameters of diastolic function, they cannot be included simultaneously in the model, as the effect of diastolic dysfunction will be spread across multiple parameters, thus causing them to appear less significant. Therefore, in addition to the baseline model of infection with hepatitis C, recipient age, MELD, and mechanical ventilation, models were formed of the baseline model with each candidate diastolic parameter: lateral $e' < 0.10$ m/s, $E/e' > 13$, $E/e' > 10$, $E/A < 1$, deceleration time < 200 ms, $LAVI > 34$ ml/m², and $LAVI > 40$ ml/m². Since each of these new models has the base model “nested” within them and the coefficients were determined via maximum likelihood, the addition of each diastolic parameter can be assessed via the likelihood ratio (LR) test. While the addition of a new coefficient (the diastolic parameter) will generally cause the model to fit the data better, whether this improved likelihood is statistically significant is unclear, and the LR test assesses this. The resulting likelihood ratios and associated p-values (the LR is distributed chi-squared) are in table 5, and the addition of parameters not involving tissue Doppler data did not statistically alter the fit of the model. While the addition of tissue Doppler alone (lateral $e' < 0.10$ m/s) had the highest LR, the introduction of either $E/e' > 10$ or $E/e' > 13$, estimates of filling pressures, to the model met statistical significance. However, since these models are not nested within each other, they cannot be directly compared with a LR test. The model with tissue Doppler had a larger C-statistic compared with the models with estimates of filling pressures, however the

difference is small, and so it is important to understand the distribution of the difference in the C-statistics, and to do this bootstrapping was utilized. A new dataset of the same size as the original was selected via sampling with replacement. Each model was fit to this new dataset and the C-statistics calculated, as were the differences in these C-statistics. This was performed 1000 times for each comparison and distributions of these differences were plotted below.



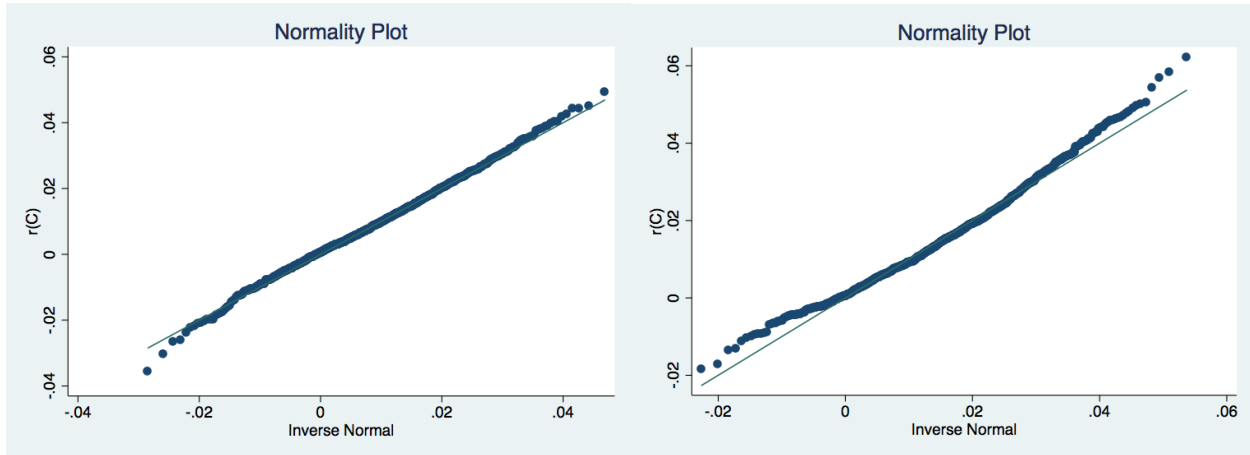
Appendix Figure 4: Distribution of the difference in Harrell's C-statistic between a model using tissue Doppler velocity for diastolic dysfunction versus $E/e' > 10$, mean of 0.0097, standard error of 0.00038



Appendix Figure 5: Distribution of the difference in Harrell's C-statistic between a model using tissue Doppler velocity for diastolic dysfunction versus $E/e' > 13$, mean of 0.0154 and standard error of 0.000392

To construct confidence intervals for the change in C-statistic, two different procedures were utilized. In the first procedure, a normal distribution was assumed, and the standard procedure for creating a 95% confidence interval was utilized ($\text{mean} \pm 1.96 \cdot \text{SE}$), giving intervals of (0.090, 0.010) and (0.014, 0.016) which would suggest that tissue Doppler caused the model to perform better than the filling pressures. This assumed a normal distribution, however, which was assessed visually with normality plots, showing the distributions to have a slight skew. In the second procedure, the differences were sorted and the upper and lower 2.5% of values were removed to create a confidence interval without respect to the underlying distribution. These intervals were (-0.010, 0.038) and (-0.0041, 0.040), suggesting that the tissue Doppler

data alone may not clearly improve the discriminatory function of the model over the filling parameters.



Appendix Figure 6: Normality plots for improvement in C statistic for tissue Doppler velocity compared with $E/e' > 10$ (left) and $E/e' > 13$ (right)

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