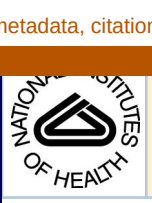

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The Impact of Left Ventricular Hypertrophy on Survival in Candidates for Liver Transplantation

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Abstract

Left ventricular hypertrophy (LVH) occurs in 12% to 30% of patients with cirrhosis; however, its prognostic significance is not well studied. We assessed the association of LVH with survival in patients undergoing a liver transplantation (LT) evaluation. We performed a multicenter cohort study of patients undergoing an evaluation for LT. LVH was defined with transthoracic echocardiography. The outcome of interest was all-cause mortality. LVH was present in 138 of 485 patients (28%). Patients with LVH were older, more likely to be male and African American, and were more likely to have hypertension. Three hundred forty-five patients did not undergo transplantation (212 declined, and 133 were waiting): 36 of 110 patients with LVH (33%) died, whereas 57 of 235 patients without LVH (24%) died ($P = 0.23$). After LT, 8 of 28 patients with LVH (29%) died over the course of 3 years, whereas 9 of 112 patients without LVH (8%) died ($P = 0.007$). This finding was independent of conventional risk factors for LVH, and all deaths for patients with LVH occurred within 9 months of LT. No clinical or demographic characteristics

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were associated with mortality among LVH patients. In conclusion, the presence of LVH is associated with an early increase in mortality after LT, and this is independent of conventional risk factors for LVH. Further studies are needed to confirm these findings and identify factors associated with mortality after transplantation to improve outcomes.

Left ventricular hypertrophy (LVH) occurs in 12% to 30% of patients with cirrhosis.[1,2] LVH appears to result in response to the hyperdynamic circulation and involves myocardial remodeling likely related to the activation of the renin-angiotensin-aldosterone axis and the increased levels of circulating bile salts, cytokines, and endotoxins in liver disease.[3-6] LVH in patients with cirrhosis may be accompanied by diastolic impairment, electrophysiological abnormalities, and a decline in systolic function—a constellation of signs called cirrhotic cardiomyopathy.[4,7]

LVH is found in 11% to 14% of the general population and is associated with older age, African American race, male sex, hypertension, a greater body mass index (BMI), and diabetes.[8-10] The presence of LVH increases the risks for cardiovascular events and mortality in the general population and in those with hypertension, end-stage renal disease, and valvular heart disease.[11-16] In addition, the presence of LVH increases mortality after renal transplantation.[17,18]

The prevalence of preexisting cardiovascular risk factors for LVH has increased in the cirrhotic population.[19,20] However, whether LVH increases mortality for patients undergoing an evaluation for liver transplantation (LT) and specifically for those undergoing LT is unknown. The aim of this study was to determine whether LVH influences mortality in a multicenter cohort of patients with cirrhosis undergoing an evaluation for LT.

Patients and Methods

Study Population

The Pulmonary Vascular Complications of Liver Disease study enrolled patients evaluated for LT at 7 centers in the United States between 2003 and 2006. The study included clinically stable outpatients undergoing an evaluation for LT because of portal hypertension with or without primary intrinsic liver disease. Patients were excluded if they had previously undergone liver or lung transplantation. Patients underwent transthoracic echocardiography as part of their LT evaluation. The study sample included patients with available echocardiography with an interpretable left ventricular mass. The study was approved by the institutional review board of each center, and all patients provided informed consent before they were enrolled into the study.

Data Collection and Variables

All patients underwent a comprehensive physical examination and laboratory assessment at their evaluation for LT. The Model for End-Stage Liver Disease (MELD) score was determined. Routine echocardio-graphic measures were obtained at accredited laboratories and were evaluated by American College of Cardiology/American Heart Association level III– trained physicians. LVH was diagnosed by the study centers on the basis of posterior

wall and interventricular septal thickness as observed on a parasternal long-axis view according to the criteria used in routine clinical practice.[21] The survival and LT status and dates were obtained from medical records, the subjects' physicians, the subjects themselves, and the Social Security Death Index as of December 31, 2006. Patients who were alive were censored at this date.

Statistical Analyses

Continuous data were summarized as medians and interquartile ranges, and comparisons between patients with LVH and patients without LVH were made with the Wilcoxon rank-sum test. Categorical data were reported as frequencies and percentages and were compared with Fisher's exact test.

The Kaplan-Meier product limit method and log-rank tests were used to determine differences in survival. Bivariate and multivariate Cox proportional hazard models were used to assess the association of LVH with the risk of death. Multiple imputations were performed for missing data before the multivariate analysis was performed. In the final multivariate model, we adjusted for variables that changed the coefficient of LVH by ≥15%, and we forced the following into the model: age, sex, race, BMI, MELD score, center, hypertension, and diabetes.

Covariates of interest that were evaluated for confounding included the following: demographics, severity of liver disease, complications of liver disease, etiology of liver disease, comorbidities, functional status [New York Heart Association (NYHA) functional class], and chronic kidney disease stage at the baseline transplant evaluation. The chronic kidney disease stage was determined with the estimated glomerular filtration rate from the Modification of Diet in Renal Disease equation.

The analysis of transplant-free survival was performed through the censoring of observations at the time of transplantation or last follow-up. Analyses of overall mortality were evaluated with adjustments for LT as a time-varying covariate.

Results

Five hundred thirty-six patients were enrolled in the Pulmonary Vascular Complications of Liver Disease study between 2003 and 2006. The study sample consisted of 485 patients with available and interpretable echocardiography. LVH was diagnosed in 138 patients (28%). Patients with LVH were older; were more often male and African American; more commonly had nonalcoholic fatty liver disease, hypertension, diabetes, and cardiopulmonary symptoms; and more often were using angiotensin-converting enzyme inhibitors (Table 1). Sixty-four percent of the LVH patients had predisposing risk factors for LVH (hypertension, diabetes, and African American race). Patients with LVH had higher systolic ($P = 0.007$) and diastolic blood pressures ($P = 0.001$) than those without LVH, although these differences were clinically insignificant. Patients with LVH were similar to those without LVH with respect to the severity of liver disease (the MELD score), the history and severity of complications of portal hypertension (variceal bleeding, ascites, and hepatocellular

carcinoma), ischemic heart disease, valvular heart disease, and the use of beta-blockers or diuretics.

During a median follow-up period of 20 months (interquartile range = 13-25 months) and 787 person-years of observation for the 485 patients evaluated for LT, 140 patients (29%) underwent transplantation, 93 (19%) died without transplantation, and 252 (52%) had not undergone transplantation as of December 31, 2006 (including 145 patients not listed for LT; Fig. 1). The 6- and 12-month overall cumulative survival rates were 92% [95% confidence interval (CI) = 89%-94%] and 86% (95% CI = 82%-88%), respectively.

There was no significant association between LVH and overall mortality (including post-LT survival) after adjustments for age, sex, race, and center [hazard ratio (HR) = 1.02 (0.61-1.72), $P = 0.92$; Fig. 2]. However, there was an apparent interaction between LVH and LT in terms of outcomes (P for interaction = 0.055). LT recipients and nonrecipients were similar in terms of age, sex, race, BMI, liver disease etiology, echocardio-graphic features, NYHA grade, and beta-blocker or diuretic use (Table 2). Although the presence of LVH was similar in the 2 groups, LT recipients were less often hypertensive ($P = 0.046$) or diabetic ($P = 0.049$) and had fewer cardiovascular symptoms than nonrecipients. LT recipients did have more severe and complicated liver disease than nonrecipients.

Among the nonrecipients, the 1-year mortality rates were similar for those with LVH [25% (95% CI: 18%- 34%)] and those without LVH [14%: 95% CI: (10%-19%); log-rank P for overall survival = 0.23; Fig. 3A)]. In contrast, LT recipients with LVH had a 1-year post-LT risk of death of 30% (16%-51%), whereas the 1-year post-LT risk of death was 7% (3%-14%) for those without LVH (log-rank P for overall post-LT survival = 0.002; Fig. 3B). A multivariate analysis revealed an approximately 4-fold greater risk for mortality after LT for those with LVH versus those without LVH (Table 3). Furthermore, an additional sensitivity analysis found no effect from excluding the single patient with portopulmonary hypertension who underwent LT on the aforementioned association (HR= 3.89, 95% CI = 1.45-10.3). When we adjusted for the potential variation between centers, we found that the association between LVH and post-LT mortality became stronger because of negative confounding by intercenter variations (HR = 5.92, 95% CI = 1.82-19.17). All deaths of LVH patients occurred within 9 months of LT.

Exploratory subgroup analyses showed no differences in demographic and clinical features between LT recipients with LVH and LT recipients without LVH (Table 4). Furthermore, there were no significant predictors of mortality for the patients with LVH who underwent LT (data not shown).

Discussion

In a multicenter cohort of patients being evaluated for LT, we showed that LVH was associated with an approximately 4-fold increase in mortality after LT. This finding was independent of the presence of conventional risk factors for LVH and other potential con-founders. The presence of LVH did not appear to affect the survival of patients who did not undergo LT (or the survival of patients before they underwent LT). A subgroup analysis of

patients with LVH who underwent LT revealed no baseline clinical or demographic characteristic associated with post-LT mortality. A similar association of LVH with postoperative cardiac events in major surgical procedures, including renal transplantation, has been previously observed.[17,18,22] The current study provides the first evidence demonstrating an association between LVH and mortality in patients with cirrhosis undergoing LT.

LVH was diagnosed in 28% of the patients evaluated for LT in our cohort. Our estimates are similar to those of previous studies, which have reported a prevalence of LVH of 12% to 30% in patients with cirrhosis.[1,2,23,24] Although we found that the majority of the LVH patients had preexisting risk factors for LVH, 36% did not. Similar observations were made by Lunseth et al.[23] in an autopsy study of patients with cirrhosis: LVH was found in 33% of patients without pathological evidence of hypertension, atherosclerosis, or other structural cardiac abnormalities. This suggests that both cirrhosis and conventional risk factors for LVH contribute to an increase in the left ventricular mass.

The approximately 4-fold increased risk for post-LT mortality in patients with LVH was observed despite adjustments for confounding by conventional risk factors for LVH, demographics, and severity of liver disease (MELD score). Furthermore, post-LT deaths of patients with LVH occurred early after LT. One potential explanation for this finding is a higher risk of peri-operative complications with LVH. However, we do not have detailed data regarding events surrounding LT in this cohort. Multiple mechanisms may underlie the cardiac dysfunction associated with LVH, including demand ischemia, arrhythmias, accelerated atherogenesis, and diastolic dysfunction.[25-27] The presence of diastolic dysfunction has been observed to increase the risk of congestive heart failure after LT[28] and has been associated with increased mortality after trans-jugular intrahepatic portosystemic shunting.[29,30] The impact of LVH before and after LT may also be influenced by medical therapies. For instance, the use of high-dose steroids and calcineurin inhibitors early after LT could exacerbate the impact of LVH and potentially explain why LVH influenced outcomes only after LT. In contrast, the use of beta-blockers and diuretics in the setting of low systemic vascular resistance before (or without) LT may diminish hemodynamic stresses on the heart and mitigate the cardiovascular consequences of LVH.

There are several limitations to this study. First, we included only patients evaluated for LT, and our findings may not be generalizable to all patients with cirrhosis. Second, we cannot eliminate the possibility that the exclusion of patients due to missing echocar-diographic or clinical data may have influenced our findings. However, the excluded patients with missing data were similar to the study cohort with respect to the recorded variables, and this lessened the chance of a selection bias (data not shown). Third, there might be differences in the criteria used to define LVH between centers that could have influenced the relationship with post-LT mortality.[31,32] However, any variability in interpretation across centers would likely have resulted in a nondifferential measurement error that would have biased our findings to the null and thereby reduced any observed association between LVH and outcomes (unless the differential classification depended on outcomes; this is difficult to conceive because echocardiography was performed before any outcomes occurred). In line with this concept, we found an increase in the HR for the association of LVH with post-LT mortality when we

accounted for centers in our multivariate analysis. Fourth, the exclusion of patients who were not listed for LT could potentially have influenced post-LT outcomes through the introduction of a selection bias. However, LVH patients who were not listed had a higher prevalence of congestive heart failure, hypertension, and chronic obstructive pulmonary disease than the listed LVH and control patients (Supporting Table 1). The exclusion of these patients would have been expected to diminish the differences in post-LT survival between the LVH and non-LVH groups and bias the results to the null. Finally, we did not collect information on the causes of death, and this potentially limited the evaluation of how LVH contributes to mortality. However, determining whether any particular cause of death is causally related to underlying LVH may not be possible. Nonetheless, this is the first large multicenter cohort study to demonstrate an association between LVH and post-LT mortality, and it supports the idea that the mechanisms for this effect require further investigation.

We observed an approximately 4-fold increase in post-LT mortality in patients with cirrhosis and LVH versus those without LVH in a large multicenter cohort, and this was independent of conventional risk factors for LVH. The temporal association of mortality with the time frame of recognized hemodynamic changes after LT raises the possibility that cardiac dysfunction may play a role. Whether increased vigilance in the follow-up of such patients in the early postoperative period may improve outcomes is not known. Further studies are needed to confirm these findings and to define the precise mechanisms involved in order to eliminate the adverse consequences of LVH on transplant outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

BMI	body mass index
CI	confidence interval
HR	hazard ratio
LT	liver transplantation
LVH	left ventricular hypertrophy
MELD	Model for End-Stage Liver Disease
NYHA	New York Heart Association

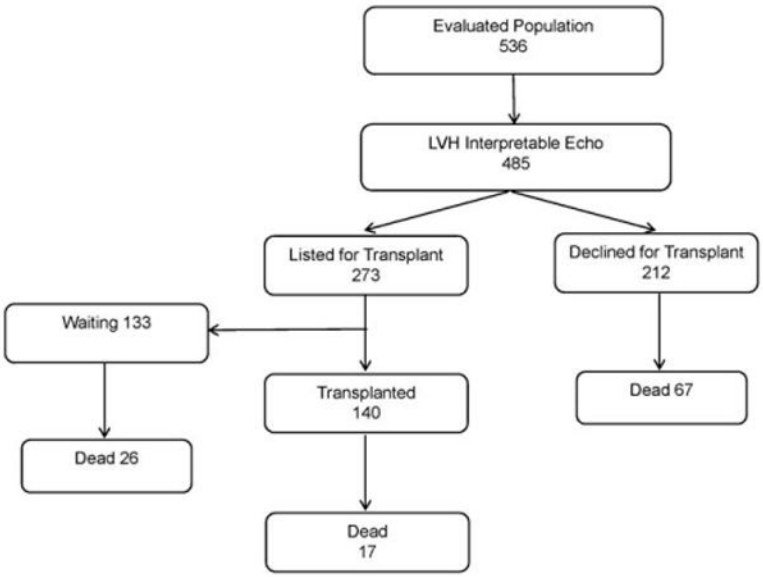

Figure 1.
Selection and outcomes of the study population.

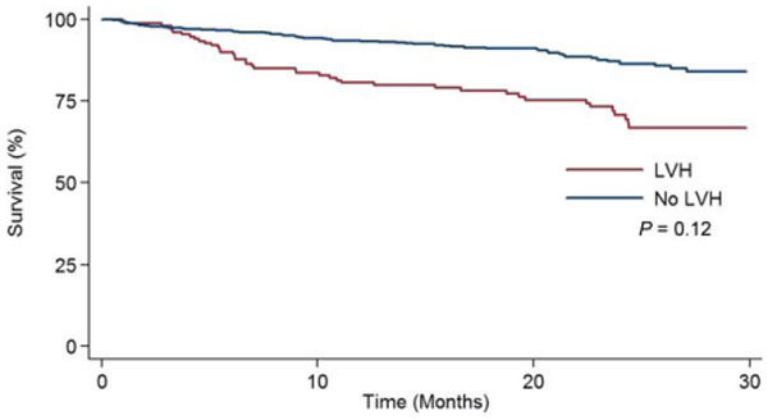

Figure 2.

Comparison of the survival of evaluated patients with LVH and evaluated patients without LVH. The survivor functions have been adjusted for race, sex, age, BMI, MELD score, hypertension, and diabetes mellitus. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

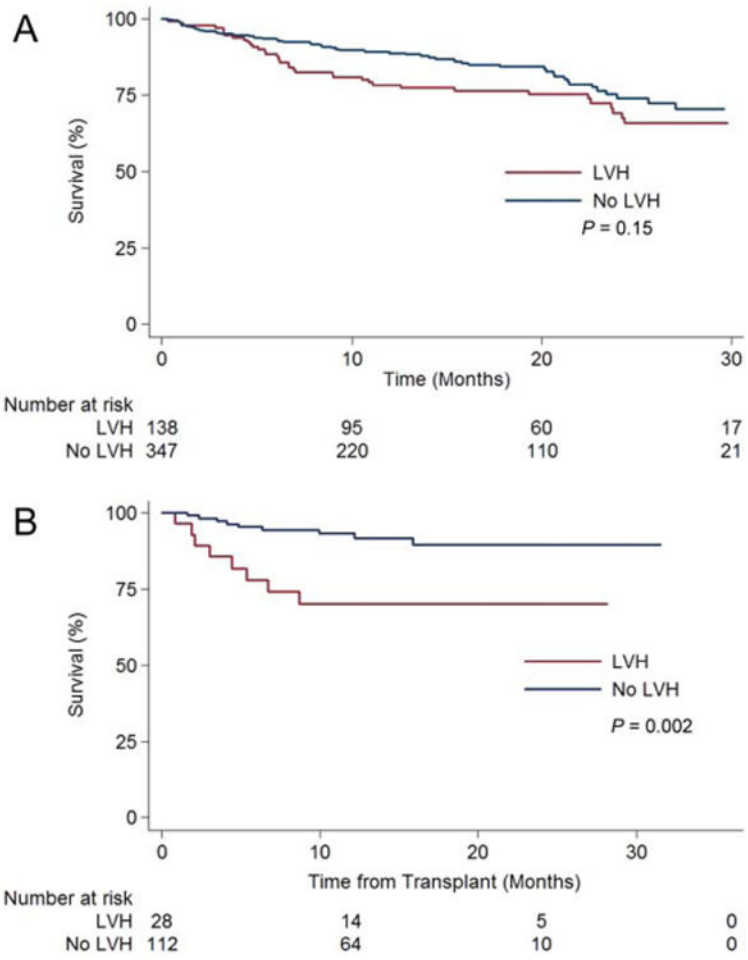

Figure 3.

(A) Comparison of the survival of patients with LVH and patients without LVH censored at the time of LT (patients not listed for LT are included). (B) Comparison of the post-LT survival of patients with LVH and patients without LVH. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table 1

Study Sample

	Sample Size (n)	LVH (n = 138)	No LVH (n5347)	*P* Value
Age (years)*	485	56 (50-61)	52 (47-58)	<0.001
Male [n (%)]	485	98 (71)	194 (56)	0.002
BMI (kg/m^2)*	483	30 (26-34)	28 (24-32)	0.001
Race [n (%)]	485			<0.001
Non-Hispanic white		119 (86)	280 (81)	
African American		12 (9)	10 (3)	
Hispanic white		4 (3)	34 (10)	
Other		3 (2)	23 (7)	
Etiology [n (%)]	485			
Alcohol		57 (41)	138 (40)	0.76
Nonalcoholic fatty liver disease		20 (14)	29 (8)	0.047
Hepatitis C virus		55 (40)	147 (42)	0.68
Other		54 (39)	109 (31)	0.11
Comorbid conditions [n (%)]				
Hypertension	483	60 (43)	81 (23)	<0.001
Diabetes mellitus	482	51 (37)	96 (28)	0.06
Coronary artery disease	483	9 (7)	6 (2)	0.38
Left ventricular dysfunction	478	26 (19)	4 (1)	0.06
Stage IV-V chronic kidney disease	485	7 (5)	10 (3)	0.27
Blood pressures (mm Hg)*				
Systolic	483	123 (110-137)	118 (106-130)	0.007
Diastolic	483	71 (65-80)	68 (60-78)	0.001
MELD score*	479	14 (10-17)	13 (10-17)	0.73
Complications of liver disease [n (%)]				
Hepatocellular carcinoma	484	10 (7)	27 (8)	1.00
Ascites	481	68 (49)	156 (45)	0.42
Variceal bleed	484	34 (25)	73 (21)	0.39
Echocardiography [n (%)]				
Left atrial size (cm)*	405	4.1 (3.8-4.5)	4 (3.6-4.6)	0.16
Aortic regurgitation: moderate to severe [n (%)]	474	5 (1)	2 (1)	1.00
Mitral regurgitation: moderate to severe [n (%)]	471	7 (5)	11 (3)	0.29
Symptoms [n (%)]				
Orthopnea	465	30 (22)	31 (9)	<0.001
Palpitation	471	29 (21)	32 (9)	0.001
Dyspnea	481	56 (41)	127 (37)	0.34
NYHA functional status grade III or higher [n (%)]	484	45 (33)	92 (27)	0.18
Medications [n (%)]				
Beta-blockers	485	56 (41)	144 (41)	0.91

	Sample Size (n)	LVH (n = 138)	No LVH (n5347)	*P* Value
Angiotensin-converting enzyme inhibitors	483	16 (12)	19 (5)	0.03
Diuretics	485	69 (50)	202 (58)	0.10

* The data are presented as medians and interquartile ranges.

Table 2

Demographic and Clinical Characteristics of the Study Population by Transplantation Status

	Sample Size (n)	Nontransplant Patients (n = 345)	Transplant Patients (n = 140)	*P* Value
Age (years)*	485	53 (48-59)	54 (48-60)	0.62
Male [n (%)]	485	199 (58)	93 (66)	0.08
BMI (kg/m^2)*	483	29 (25-33)	28 (24-31)	0.18
Race [n (%)]	485			0.69
African American		15 (4)	7 (5)	
Non-Hispanic white		288 (83)	111 (79)	
Hispanic white		25 (7)	13 (9)	
Other		17 (5)	9 (6)	
Etiology of liver disease [n (%)]	485			
Alcohol		143 (41)	52 (37)	0.41
Nonalcoholic fatty liver disease		33 (10)	16 (11)	0.51
Hepatitis C virus		143 (41)	59 (42)	0.91
Other		120 (35)	43 (31)	0.46
Comorbid conditions [n (%)]				
Hypertension	483	110 (32)	31 (22)	0.046
Diabetes mellitus	482	114 (33)	33 (24)	0.049
Chronic obstructive pulmonary disease	483	27 (8)	8 (6)	0.56
Coronary artery disease	483	13 (4)	2 (1)	0.25
Left ventricular dysfunction	478	21 (6)	9 (6)	0.84
Stage IV-V chronic kidney disease	484	8 (2)	9 (6)	0.052
Blood pressures (mm Hg)*				
Systolic	483	120 (110-132)	117 (104-129)	0.029
Diastolic	483	70 (62-79)	68 (60-75)	0.045
MELD score*	479	12 (10-16)	14 (11-18)	<0.001
Complications of cirrhosis [n (%)]				
Hepatocellular carcinoma	484	19 (6)	18 (13)	0.008
Ascites	477	118 (34)	69 (49)	0.003
Variceal bleed	484	78 (23)	29 (21)	0.71
Encephalopathy	483	138 (40)	67 (48)	0.13
Echocardiography [n (%)]				
Left atrial size (cm)*	405	4.1 (3.7- 4.5)	4.1 (3.6-4.5)	0.79
Aortic regurgitation [n (%)]	473	86 (25)	32 (23)	0.72
Aortic regurgitation: moderate to severe [n (%)]	473	4 (1)	2 (1)	1.00
Mitral regurgitation: moderate to severe [n (%)]	471	14 (4)	4 (3)	0.8
LVH [n (%)]	485	110 (32)	28 (20)	0.10
Symptoms [n (%)]				
Palpitation	471	53 (15)	8 (6)	0.004

	Sample Size (n)	Nontransplant Patients (n = 345)	Transplant Patients (n = 140)	*P* Value
Orthopnea	465	47 (14)	14 (10)	0.44
Dyspnea	481	137 (40)	46 (33)	0.21
NYHA functional status III or higher [n (%)]	484	104 (30)	33 (24)	0.15
Medications [n (%)]				
Beta-blockers	485	147 (43)	53 (38)	0.36
Angiotensin-converting enzyme inhibitors	483	30 (9)	5 (4)	0.05
Diuretics	485	193 (56)	78 (56)	1.00
Deaths [n (%)]	485	93 (27)	17 (12)	<0.001

* The data are presented as medians and interquartile ranges.

Table 3

Posttransplant Mortality (n = 140)

	HR	95% CI	*P* Value
LVH adjusted for age, sex, race, and BMI	3.72	1.39-10.00	0.009
LVH adjusted for age, sex, race, BMI, and MELD score	3.73	1.39-10.05	0.009
LVH adjusted for age, sex, race, BMI, MELD score, and center	5.92	1.82-19.17	0.003

Table 4

Transplant Population

	Sample Size (n)	LVH (n = 28)	No LVH (n = 112)	*P* Value
Age (years)*	140	57 (52-61)	53 (47-60)	0.14
Male [n (%)]	140	21 (75)	72 (64)	0.37
BMI (kg/m^2)*	140	28 (26-32)	28 (24-31)	0.28
Race [n (%)]	140			0.19
African American		3 (11)	4 (4)	
Non-Hispanic white		23 (82)	88 (79)	
Hispanic white		2 (7)	11 (10)	
Other race		0 (0)	9 (8)	
Etiology of liver disease [n (%)]	140			
Alcohol		14 (50)	38 (34)	0.13
Nonalcoholic fatty liver disease		5 (18)	11 (10)	0.31
Hepatitis C virus		9 (32)	50 (45)	0.29
Other		12 (43)	31 (28)	0.17
Comorbid conditions [n (%)]				
Hypertension	138	8 (29)	23 (20)	0.45
Diabetes mellitus	138	9 (32)	24 (21)	0.32
Coronary artery disease	138	0 (0)	2 (2)	1.00
Left ventricular dysfunction	138	9 (8)	0 (0)	0.20
Stage IV-V chronic kidney disease	140	3 (11)	6 (5)	0.38
Blood pressures (mm Hg)*				
Systolic	140	120 (105-136)	116 (103-128)	0.24
Diastolic	140	68 (62-72)	68 (60-76)	0.93
MELD score*	137	14 (11-19)	14.5 (11-18)	0.98
Complications of liver disease [n (%)]				
Hepatocellular carcinoma	140	4 (14)	14 (12)	0.76
Ascites	139	15 (54)	60 (54)	1.00
Variceal bleed	140	7 (25)	22 (20)	0.6
Portopulmonary hypertension	71	0 (0)	1 (0.9)	1.00
Right ventricular hypertrophy [n (%)]	139	8 (29)	5 (4)	0.001
Symptoms [n (%)]				
Palpitation	133	3 (11)	5 (4)	0.17
Orthopnea	129	5 (18)	9 (8)	0.14
Dyspnea	137	8 (29)	38 (34)	1.00
NYHA functional status III or higher [n (%)]	140	8 (29)	25 (22)	0.47
Medications [n (%)]				
Beta-blockers	140	9 (32)	44 (39)	0.52
Angiotensin-converting enzyme inhibitors	138	2 (7)	3 (3)	0.27
Diuretics	140	12 (43)	66 (59)	0.14

	Sample Size (n)	LVH (n = 28)	No LVH (n = 112)	*P* Value
Deaths [n (%)]	140	8 (29)	9 (8)	0.007

* The data are presented as medians and interquartile ranges.