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Prognostic Value of RV Function Before and After Lung Transplantation

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CME Objective for This Article: After reading this article the reader should understand: 1) the prognostic importance of several variables "pre" lung transplantation; 2) the prognostic importance of several variables "post" lung transplantation; and 3) the current information pertaining to post-lung transplantation right ventricular longitudinal strain and pulmonary arterial systolic pressure to help stratify mortality risk in patients following lung transplantation.

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ABSTRACT

OBJECTIVES We investigated the effects of lung transplantation on right ventricular (RV) function as well as the prognostic value of pre- and post-transplantation RV function.

BACKGROUND Although lung transplantation success has improved over recent decades, outcomes remain a challenge. Identifying predictors of mortality in lung transplant recipients may lead to improved long-term outcomes after lung transplantation.

METHODS Eighty-nine (age 60 ± 6 years, 58 men) consecutive patients who underwent single or double lung transplantation and had pre- and post-transplantation echocardiograms between July 2001 and August 2012 were evaluated. Echocardiographic measurements were performed before and after lung transplantation. Left ventricular (LV) and RV longitudinal strains were analyzed using velocity vector imaging. Cox proportional prognostic hazard models predicting all-cause death were built.

RESULTS There were 46 all-cause (52%) and 17 cardiac (19%) deaths during 43 ± 33 months of follow-up. After lung transplantation, echocardiography showed improved systolic pulmonary artery pressure (SPAP) (50 ± 19 mm Hg to 40 ± 13 mm Hg) and RV strain (−17 ± 5% to −18 ± 4%). No pre-transplantation RV parameter predicted all-cause mortality. After adjustment for age, sex, surgery type, and etiology of lung disease in a Cox proportional hazards model, both post-transplantation RV strain (hazard ratio: 1.13, 95% confidence interval: 1.04 to 1.23, $p = 0.005$), and post-transplantation SPAP (hazard ratio: 1.03, 95% confidence interval: 1.01 to 1.05, $p = 0.011$) were independent predictors of all-cause mortality. When post-transplantation RV strain and post-transplantation SPAP were added the clinical predictive model based on age, sex, surgery type, and etiology, the C-statistic improves from 0.60 to 0.80 ($p = 0.002$).

CONCLUSIONS Alterations of RV function and pulmonary artery pressure normalize, and post-transplantation RV function may provide prognostic data in patients after lung transplantation. Our study is based on a highly and retrospectively selected group. We believe that larger prospective studies are warranted to confirm this result.
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Lung transplantation (LTx) is a treatment option for patients with a range of end-stage lung pathologies. Although outcomes have improved over the past several decades, at least in part due to immunosuppressive medications, LTx outcomes remain among the worst overall for organ transplantation (1,2), Identifying predictors of mortality in lung transplant recipients is an important issue, with the goal of improving long-term outcomes in these patients. In a large cohort study, pulmonary hypertension (PHT) before LTx has been shown to be a prognostic factor in post-LTx survival in a univariate analysis (3). The effects of advanced PHT on cardiac anatomy and physiology are diverse, including right ventricular (RV) dilation and hypertrophy, tricuspid regurgitation (TR), and interventricular septum deviation, with consequent impact on cardiac function (4). Therefore, the evaluation of PHT in the absence of knowledge of related cardiac changes, in particular RV function, may be problematic. Recent work has shown that direct measurement of RV function with strain imaging (RV strain) is related to outcome in valve disease and end-stage heart failure (5-7). In addition, successful LTx may lead to normalization of RV morphology and function, and the prognostic value of RV morphology and function before and after

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LTx has not been well characterized (8,9). We hypothesized that LTx leads to normalization of both RV strain and pulmonary artery pressure and that improvement of both RV strain and pulmonary artery pressure (PAP) would result in a good outcome. In this study, we investigated the effects of LTx on RV function as well as the prognostic value of pre- and post-transplantation RV function.

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

HR = hazard ratio

LA = left atrial

LTx = lung transplantation

LV = left ventricular

PAP = pulmonary artery pressure

PHT = pulmonary hypertension

PVR = pulmonary vascular resistance

RV = right ventricular

RVEDA = right ventricular end-diastolic area

RVFAC = right ventricular fractional area change

SPAP = systolic pulmonary artery pressure

TR = tricuspid regurgitation

METHODS

STUDY POPULATION. This was a retrospective observational cohort study. Between July 2001 and August 2012, a total of 933 patients underwent primary LTx for end-stage lung disease at our institution. Although there is standardized clinical follow-up for all patients after LTx, echocardiography is obtained only in those patients with cardiac history or a clinical indication. Therefore, we identified 95 consecutive patients who had an echocardiogram at baseline (within 3 months before LTx) and at follow-up (at least 3 months after LTx) for inclusion in the study. Six patients were excluded because of poor image quality and low frame rate defined as <40 frame/s. Therefore, 89 patients were included for the final analysis. Based on an assumed rate of death of ~60% during a follow-up period, we anticipated 83 patients would be needed to develop a stable statistical model with 5 variables (10). Given the retrospective nature of the study, the Cleveland Clinic Institutional Review Board approved waiver of patient consent because we minimized risk by de-identifying protected health data. Recipient and surgery data were extracted from the Unified Transplant Database. Also, a supplemental review of medical records was performed.

CLINICAL OUTCOMES. All-cause mortality was the primary endpoint. Death notification was confirmed by observation of a death certificate or verified by a family member. The duration of follow-up was started at the time of the follow-up echocardiogram and ended in June 2013. The secondary endpoint was cardiovascular death. Cardiovascular death included death due to heart failure and sudden cardiac death (including sudden death at home).

LEFT VENTRICULAR FUNCTION. All patients underwent comprehensive echocardiography performed by dedicated cardiac sonographers with commercially available instruments (Philips Medical Systems, NA, Bothell, Washington; General Electric Medical Systems, Milwaukee, Wisconsin; and Siemens Medical Solutions USA, Inc., Malvern, Pennsylvania) as part of a standard clinical diagnostic evaluation before and after LTx. Measurements and recordings were obtained according to the American Society of Echocardiography recommendations (11). Left ventricular (LV) end-diastolic volume, LV end-systolic volume, and left atrial (LA) volume were calculated by the Simpson method using 2-dimensional images and indexed to body surface area. Stroke volume was calculated as the product of the cross-sectional area of the LV outflow tract and the time-velocity integral in the LV outflow tract. The transmitral early diastolic velocity (E) and peak atrial filling velocity (A) were acquired in the apical 4-chamber view. The early diastolic (e′) mitral annular tissue velocity was also measured in the apical 4-chamber view with the sample volume positioned at both the septal and lateral mitral annuli; we used the average values of these 2 positions. LV peak longitudinal strain measurements were obtained from gray-scale images recorded in the apical 4-chamber, 2-chamber, and long-axis views. The frame rate was maintained at a level >40 and <80 frame/s. LV strain was analyzed offline using velocity vector imaging (Syngo VVI, Siemens Medical Solutions, Mountain View, California) (6). Good image quality was defined as clear detection of the endocardial border throughout the cardiac cycle, and regions of interest at the apex and annulus were ensured. After manual definition of the LV endocardial border, the endocardium was automatically tracked throughout the cardiac cycle. Global LV strain was obtained by averaging all segmental strain values from the apical 4-chamber, 2-chamber, and long-axis views.

RV FUNCTION. Standard echocardiographic measurements of the right ventricle were made in accordance with current guidelines (12). Right ventricular fractional area change (RVFAC) was defined using the formula: (end-diastolic area − end-systolic area)/end-diastolic area × 100. Tricuspid annular plane systolic excursion was measured as the distance of systolic movement of the anterior tricuspid annulus toward the RV apex using 2-dimensional images. Systolic pulmonary artery pressure (SPAP) was estimated from the maximal continuous-wave Doppler velocity of the TR jet using systolic transtricuspid pressure gradient calculated by the modified Bernoulli equation and the addition of estimated right atrial pressure as previously described (13). An index of pulmonary vascular resistance (PVR) was derived by dividing the maximal velocity of the TR jet by the RV outflow tract time-velocity integral. RV strain was measured offline (Syngo VVI) (6). Likewise, good image quality in RV assessment was defined as clear detection of the endocardial border throughout the cardiac cycle. The endocardial border of the RV was traced from an apical 4-chamber view, and segmental strain curves were generated automatically. Peak strain for the 3 RV free wall segments was averaged to produce global RV longitudinal strain, with exclusion of the interventricular septum to avoid LV interaction (6,7,14) (**Figure 1**, Online Video 1, Online Figure 1). All measurements were made offline by an investigator blinded to all clinical and demographic information and were performed and averaged over 3 cardiac cycles.

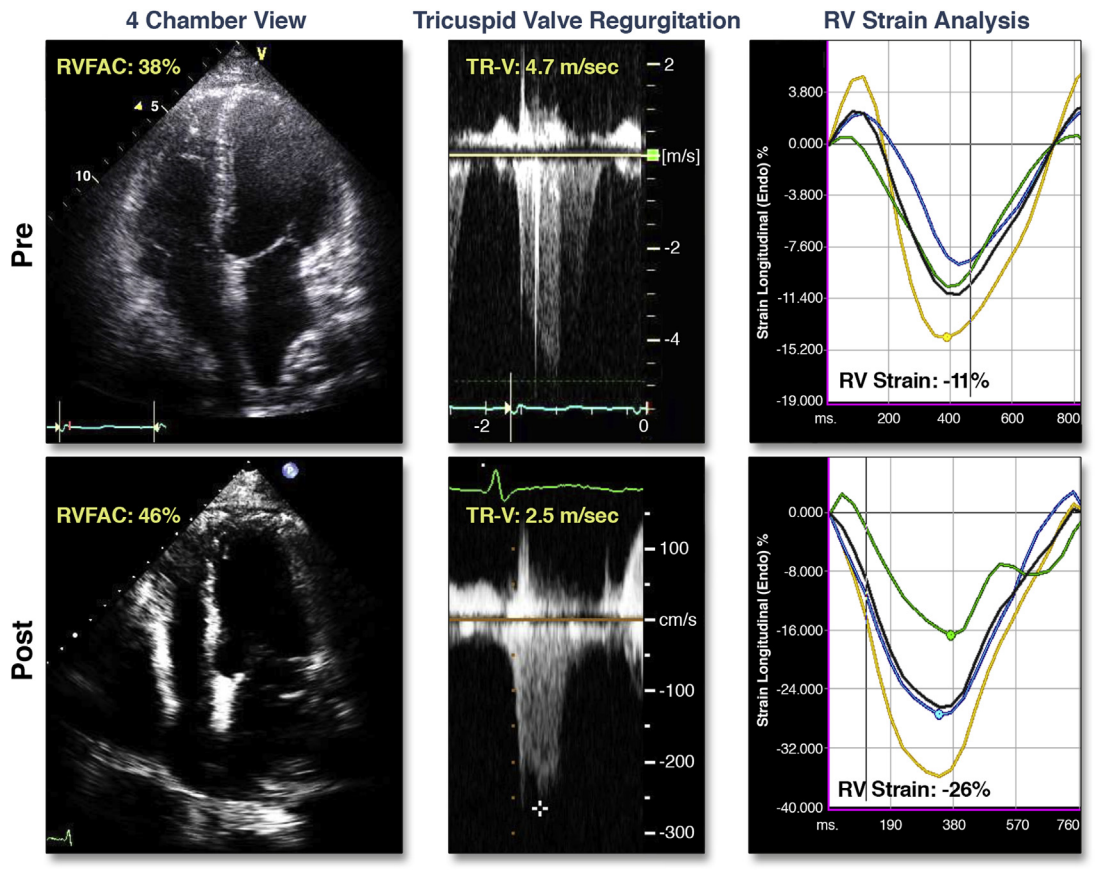


FIGURE 1 Images Before and After Lung Transplantation

Before lung transplantation, right ventricular fractional area change (RVFAC) and right ventricular (RV) strain were depressed and tricuspid valve regurgitation velocity (TR-V) was accelerated. After lung transplantation, these variables improved. Online Video 1 shows the RV strain curve from a post-operative echocardiogram.

PULMONARY PATHOLOGY. The pathological analysis of all explanted lungs was reviewed to categorize lung pathology in all cases according to guidelines. The pulmonary fibrosis disease group was identified by usual interstitial pneumonia in pathology (15). The chronic obstructive pulmonary disease group was identified by emphysema in pathology (16).

STATISTICAL ANALYSIS. Data are presented as mean ± SD if the Kolmogorov-Smirnov test showed a normal distribution. Otherwise, the median and interquartile ranges were used. Comparisons between before and after LTx data were performed by paired Student *t* test. Median values of RV strain (pre: −16% and post: −18%) and SPAP (pre: 47 mm Hg and post: 39 mm Hg) were used to divide patients into 2 equal groups for Kaplan-Meier analysis, with survival compared using a 2-sided log-rank test. The association of echocardiographic parameters with outcome was identified by Cox proportional hazards models in univariable and multivariable analyses. Variables with a univariable value of $p < 0.10$ after adjustment for age and sex were incorporated into the multivariable models. In addition, surgery type (single or double LTx) and etiology (idiopathic pulmonary fibrosis or not) were incorporated into the final model because this factor is a marker for a high-risk group of patients (17). To avoid collinearity in situations in which >1 variable measured the same physiological parameter (e.g., RVFAC and RV strain as markers of RV systolic function), separate models were created for each categorical variable (LV variables and RV variables). A hazard ratio (HR) with a 95% confidence interval (CI) was calculated for each variable. The assumption of proportional hazards was assessed by plotting the scaled Schoenfeld residuals for each independent variable against time; these correlations

were found to be nonsignificant. We performed analysis stratified by echocardiographic variables for interaction and found no evidence of interaction in our final model. Sequential Cox models were performed to determine the incremental prognostic benefit of echocardiographic parameters over clinical data, with an incremental prognostic value being defined by a significant increase in global chi-square. Net reclassification index was evaluated to assess the incremental benefit of adding post-RV strain and post-transplantation SPAP to the baseline model (age, sex, surgery type, and etiology). To evaluate the predictive ability of our model, we used Harrell's C concordance statistic calculated. The method of DeLong was used to study differences in C-index (18). Receiver-operating characteristic curves were generated to determine optimal cutoff values of continuous variables. The best cutoff value was defined as the upper limit of the CI of the Youden index. To validate SPAP estimation by echocardiography, we used data from 35 patients from our series of 95 patients who also had a right heart catheterization performed within 7 days to assess PAP. RV strain for each patient was performed in a blinded manner by 3 independent observers. Each observer performed 2 independent measurements of RV strain values on the same echocardiographic images in a randomly selected group of 9 patients (3 patients with excellent image quality, 3 patients with good image quality, and 3 patients with poor image quality). Variability was tested with 2-way analysis of variance with calculation of intraobserver and interobserver standard error of the mean (SEM_{intra} and SEM_{inter}). SEM_{intra} expresses the random error by a single observer, whereas SEM_{inter} is an indicator of the mean variation between different observers. Statistical analysis was performed using standard statistical software packages (SPSS version 20.0, SPSS Inc., Chicago, Illinois and R software version 2.12.0, R Project, Vienna, Austria), and statistical significance was defined as $p < 0.05$.

TABLE 1 Baseline Clinical Variables (N = 89)

Age, yrs	61 ± 6
Male	58 (65)
Body surface area, m^2	1.9 ± 0.2
Heart rate, beats/min	79 ± 13
Systolic blood pressure, mm Hg	127 ± 16
Diastolic blood pressure, mm Hg	71 ± 9
Diagnosis	
COPD (emphysema)	41 (46)
Pulmonary fibrosis (usual interstitial pneumonia)	48 (54)
Comorbidities	
Hypertension	38 (43)
Coronary artery disease	17 (19)
Diabetes mellitus	24 (27)
Surgery	
Single-lung transplantation	49 (55)
Invasive hemodynamic data	
Right atrial pressure, mm Hg	7 ± 4
Pulmonary capillary wedge pressure, mm Hg	12 ± 7
Systolic pulmonary artery pressure, mm Hg	48 ± 13
Cardiac output (Fick), l/min	5 ± 2

Values are mean ± SD or n (%).
COPD = chronic pulmonary obstructive disease.

RESULTS

STUDY POPULATION. Baseline clinical and hemodynamic variables are shown in Table 1. The mean age of the 31 female and 58 male patients was 61 years. All patients were in New York Heart Association functional class III or IV. Pathological analysis revealed that there were 48 pulmonary fibrosis patients (54%) and 41 patients (46%) with chronic obstructive pulmonary disease. There were 49 (55%) single LTx patients and 41 (45%) double LTx patients. There were comorbidities in this group, mainly patients with hypertension (43%).

TABLE 2 Baseline (Pre) and After Transplantation (Post) Echocardiography Data

LV Function	Pre	Post	p Value
LVEDV, ml	84 ± 26	95 ± 30	**0.001**
LVESV, ml	34 ± 14	37 ± 16	**0.017**
LVSV, ml	50 ± 16	58 ± 18	**<0.001**
LVEF, %	60 ± 7	61 ± 7	0.129
LAVi, ml	43 ± 17	54 ± 19	**<0.001**
E/A ratio	0.9 ± 0.3	1.2 ± 0.7	**<0.001**
E/e′ ratio	8.8 ± 3.2	10.2 ± 3.6	**0.007**
RV function			
RVEDA, cm^2	22 ± 7	20 ± 5	**0.016**
RVESA, cm^2	13 ± 5	11 ± 3	**<0.001**
RVFAC, %	40 ± 6	43 ± 6	**<0.001**
RA area, cm^2	14 ± 4	15 ± 4	**0.047**
TAPSE, cm	1.8 ± 0.3	1.9 ± 0.4	0.123
SPAP, mm Hg	50 ± 19	40 ± 13	**<0.001**
PVR, Wood units	2.3 ± 0.9	1.8 ± 0.5	**<0.001**
IVC, cm	1.5 ± 0.4	1.6 ± 0.4	0.138
Strain, %			
LV	−16 ± 3	−16 ± 3	0.158
RV	−17 ± 5	−19 ± 4	**0.011**

Values are mean ± SD. **Bold** indicates p ≤ 0.05.
A-wave = transmitral atrial filling wave; e′ velocity = early diastolic mitral annular tissue velocity; E-wave = transmitral early diastolic wave; IVC = inferior vena cava; LAVi = left atrial volume index; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LVSV = left ventricular systolic volume; PVR = pulmonary vascular resistance; RA = right atrial; RV = right ventricular; RVEDA = right ventricular end-diastolic area; RVESA = right ventricular end-systolic area; RVFAC = right ventricular fractional area change; SPAP = systolic pulmonary artery pressure; TAPSE = tricuspid annular plane systolic excursion.

EFFECT OF LTX ON CARDIAC FUNCTION. The median time from preoperative echocardiography to surgery was 1 month (range 0 to 3 months). The median time to follow-up echocardiography was 11 months (range 3 to 60 months). Echocardiographic variables before and after LTx are shown in Table 2. There were no significant differences in LV ejection fraction, right atrial area, tricuspid annular plane systolic excursion, inferior vena cava, and LV strain before and after LTx (all $p > 0.05$), whereas LV end-diastolic volume ($p = 0.007$), LV stroke volume ($p = 0.006$), and LA volume ($p < 0.001$) significantly increased after LTx. E/A ratio ($p = 0.001$) and E/e′ ($p = 0.007$) ratio also increased after LTx. For the RV functional variables, the RV areas ($p = 0.033$ and $p < 0.001$), SPAP ($p < 0.001$), and PVR ($p < 0.001$) significantly decreased, whereas RVFAC ($p < 0.001$) and RV strain improved ($p = 0.021$). Echocardiographic characteristics stratified by etiology and high PAP are shown in Table 3. In both the chronic obstructive pulmonary disease and pulmonary fibrosis groups, LTx led to improvement in RV systolic function (RVFAC) and a concomitant increase in LV stroke volume and LV pre-load (quantified as LA volume). Interestingly, the patients' pre-transplantation SPAP influenced the post-transplantation improvement of RV function (Table 3). Especially in higher PAP before transplantation, LTx led to diminished right atrial and RV size, and improvement in RV systolic function (RVFAC and RV strain) and hemodynamic parameters (SPAP and PVR).

EVENT-FREE SURVIVAL. Over a period of 43 ± 33 months (range 5 to 137 months), 46 (52%) patients reached the primary endpoint (all-cause death) and 17 (19%) patients reached the secondary endpoint (cardiovascular death). The causes of death were sepsis/multisystem organ failure (n = 14, 30%), respiratory infection (n = 9, 19%), chronic rejection (n = 5, 11%), malignancy (n = 1, 2%), heart failure (n = 12, 26%), and sudden cardiac death (n = 5, 10%). Figure 2 illustrates the event-free survival of patients after LTx stratified according to median values of RV strain and SPAP. Patients with RV abnormality (RV strain ≥−18% [median value]) and PAP abnormality (SPAP ≥39 mm Hg [median value]) had significantly shorter event-free survival than those without these abnormalities; the 3-year event-free survival rates in patients without post-transplantation RV abnormality or PAP abnormality and in patients with post-transplantation RV and PAP abnormalities were 73% and 36%, respectively ($p < 0.001$).

PREDICTING EVENT-FREE SURVIVAL. E/e′ at baseline, RV end-diastolic area (RVEDA), SPAP, LV strain, and RV strain after LTx were associated with all-cause death, independent of age and sex. In addition, LA volume, E/e′ and RVEDA at baseline, and SPAP, PVR and RV strain after LTx were also associated with cardiac death, independent of age and sex (Table 4). Interestingly, there were no pre-transplantation RV parameters to predict all-cause mortality. In multivariable Cox proportional hazards models, LV strain at baseline (HR: 1.23, 95% CI: 1.00 to 1.52, $p = 0.05$, model 1), SPAP after LTx (HR: 1.03, 95% CI: 1.01 to 1.05, $p = 0.011$, model 2), and RV strain after LTx (HR: 1.13, 95% CI: 1.04 to 1.23, $p = 0.005$, model 2) were independently associated with all-cause death. Even after adjustment for the time interval of post-LTx, the results remained the same (SPAP after LTx,

TABLE 3 Baseline (Pre) and After Transplantation (Post) in Echocardiography, Stratified by Etiology and Pulmonary Hypertension

	Pre	Post	p Value	Pre	Post	p Value
	COPD (Emphysema)			Pulmonary Fibrosis		
LVEDV, ml	83 ± 27	100 ± 25	**<0.001**	85 ± 26	90 ± 34	0.148
LVESV, ml	33 ± 14	40 ± 15	**0.006**	34 ± 14	34 ± 17	0.426
LVSV, ml	50 ± 17	60 ± 15	**0.001**	50 ± 15	57 ± 20	**0.028**
LVEF, %	61 ± 8	60 ± 8	0.289	60 ± 7	63 ± 7	**0.007**
LAVi, ml	37 ± 16	56 ± 18	**<0.001**	48 ± 16	53 ± 20	0.053
E/A ratio	1.0 ± 0.4	1.3 ± 0.9	**0.016**	1.0 ± 0.4	1.1 ± 0.4	**0.003**
E/e′ ratio	8.4 ± 2.9	10.4 ± 4.0	**0.018**	9.0 ± 3.3	10.0 ± 3.2	**0.044**
RVEDA, cm^2	19 ± 7	20 ± 5	0.339	23 ± 6	20 ± 4	**<0.001**
RVESA, cm^2	12 ± 6	11 ± 4	0.299	14 ± 4	11 ± 2	**<0.001**
RVFAC, %	40 ± 6	43 ± 6	**0.012**	39 ± 6	43 ± 5	**<0.001**
SPAP, mm Hg	47 ± 16	39 ± 11	**0.002**	52 ± 20	42 ± 14	**<0.001**
PVR, Wood units	2.2 ± 0.9	1.8 ± 0.6	**0.003**	2.4 ± 0.9	1.8 ± 0.5	**<0.001**
LV strain, %	−15 ± 3	−15 ± 3	0.422	−16 ± 3	−17 ± 3	0.105
RV strain, %	−17 ± 3	−18 ± 4	0.224	−16 ± 4	−18 ± 4	**0.007**
	High SPAP (>Median Value of SPAP)			Low SPAP (≤Median Value of SPAP)		
LVEDV, ml	80 ± 21	94 ± 28	**0.002**	87 ± 30	95 ± 33	0.074
LVESV, ml	32 ± 12	36 ± 33	0.069	35 ± 16	38 ± 18	0.138
LVSV, ml	48 ± 13	57 ± 18	**<0.001**	52 ± 18	58 ± 18	**0.049**
LVEF, %	60 ± 8	61 ± 8	0.185	62 ± 7	61 ± 7	0.249
LAVi, ml	40 ± 16	52 ± 19	**<0.001**	45 ± 18	56 ± 20	**<0.001**
E/A ratio	0.9 ± 0.3	1.1 ± 0.6	**<0.001**	0.9 ± 0.4	1.2 ± 0.8	**0.013**
E/e′ ratio	8.3 ± 2.4	10.4 ± 4.4	**0.003**	9.2 ± 3.2	10.0 ± 2.8	0.119
RVEDA, cm^2	19 ± 6	19 ± 4	0.445	23 ± 7	20 ± 5	**0.006**
RVESA, cm^2	11 ± 4	11 ± 3	0.278	15 ± 7	12 ± 3	**<0.001**
RVFAC, %	42 ± 5	43 ± 5	0.101	38 ± 7	43 ± 7	**<0.001**
SPAP, mm Hg	36 ± 7	38 ± 11	0.107	63 ± 17	43 ± 14	**<0.001**
PVR, Wood units	1.8 ± 0.6	1.7 ± 0.4	0.288	2.7 ± 0.9	1.8 ± 0.5	**<0.001**
LV strain, %	−15 ± 3	−16 ± 3	0.136	−16 ± 3	−16 ± 3	0.367
RV strain, %	−17 ± 5	−18 ± 4	0.308	−16 ± 4	−18 ± 4	**0.006**

Values are mean ± SD. **Bold** indicates p value ≤0.05.
Abbreviations as in Tables 1 and 2.

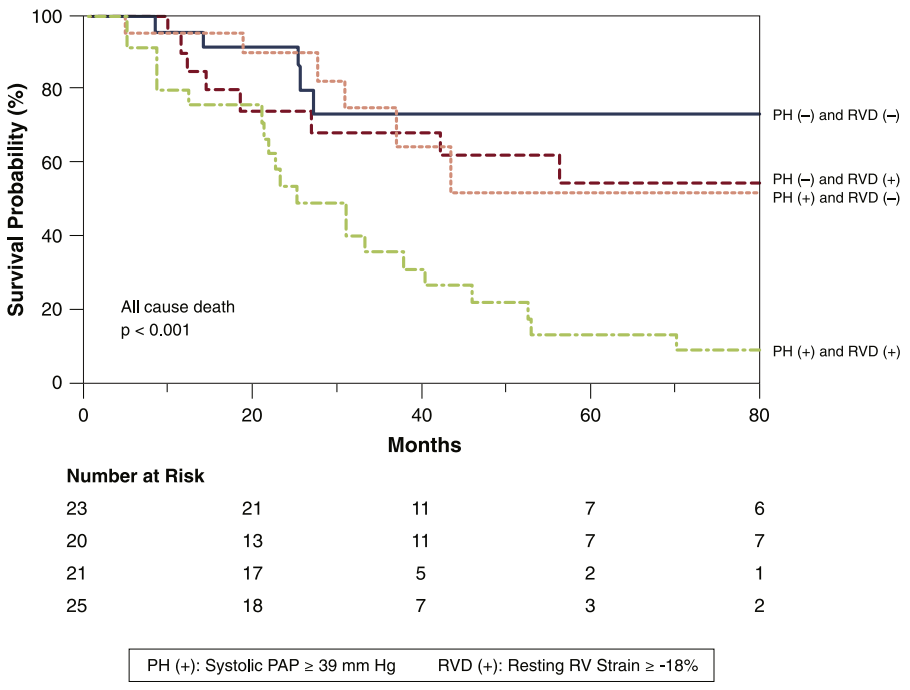


FIGURE 2 Kaplan-Meier Analysis of Event-Free Survival After Lung Transplantation

Patients were stratified according to high pulmonary artery pressure (PH) and right ventricular abnormality. PAP = pulmonary artery pressure; RV = right ventricular; RVD = right ventricular dysfunction.

HR: 1.03, 95% CI: 1.01 to 1.06, p = 0.023, model 3; RV strain after LTx, HR: 1.16, 95% CI: 1.07 to 1.26, p = 0.001, model 3) (Table 5). The incremental benefit of echocardiographic parameters in the prediction of events is shown in Figure 3. The addition of echocardiographic parameters significantly improved the prognostic power of a model containing clinical variables (model 1: age, sex, surgery type, and etiology, chi-square = 1.6; model 2: plus LV strain as an LV function, chi-square = 8.4, p = 0.011; model 3: plus SPAP as an RV afterload parameter, chi-square = 16.8, p = 0.010; model 4: plus RV strain as an RV function, chi-square = 24.0, p = 0.011). The combination of post-transplantation RV strain + post-transplantation SPAP with the baseline model (age, sex, surgery type, and etiology) led to a significant reclassification improvement (net reclassification index: 0.53 [0.22 to 0.84], p < 0.001). Furthermore, for our Cox model based on age, sex, surgery type, and etiology, the Harrell C concordance statistic was calculated to be 0.60. When post-transplantation RV strain and post-transplantation SPAP are added to the models, the C-statistic improves to 0.80 (p = 0.002). The area under the receiver-operating characteristic curve was used to designate the best cutoff values to predict the occurrence of events, namely, post-transplantation SPAP >45 mm Hg (area under the receiver-operating characteristic curve 0.65, p = 0.01), and post-transplantation RV strain >−17% (area under the receiver-operating characteristic curve: 0.77, p < 0.001).

ACCURACY AND VARIABILITY FOR ECHOCARDIOGRAPHIC PARAMETERS. There was a good correlation between SPAP obtained by echocardiography and right heart catheterization (r = 0.86, p < 0.001) (Online Figure 2), similar to the finding of recent investigators (19). In the excellent image quality group, SEM_{intra} was 0.9% and SEM_{inter} was 1.2%. In the good image quality group, SEM_{intra} was 1.1% and SEM_{inter} was 1.4%. Finally, in the poor image quality group, SEM_{intra} was 2.8% and SEM_{inter} was 3.9%. We included only excellent and good image quality data in the final cohort.

DISCUSSION

After LTx, increased LV and LA size was noted, as was increased LV filling pressure (E/A and E/e′ ratios), alteration of RV size (RVEDA and RV end-systolic area), function (RVFAC and RV strain), and

TABLE 4 Univariable Associations of All-Cause Death and Cardiac Death

	All-Cause Death		Cardiac Death	
	Adjustment for Age and Sex		Adjustment for Age and Sex	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Baseline				
LVEDV	1.01 (0.99–1.02)	0.55	1.01 (0.99–1.03)	0.31
LVSV	1.01 (0.99–1.03)	0.35	1.02 (0.98–1.06)	0.18
LVEF	1.03 (0.98–1.07)	0.23	1.04 (0.97–1.12)	0.27
LAVi	1.01 (0.99–1.03)	0.37	1.03 (1.00–1.06)	**0.03**
E/A	0.92 (0.36–2.35)	0.86	2.51 (0.80–7.86)	0.11
E/e′	1.15 (1.00–1.33)	**0.05**	1.32 (1.09–1.59)	**0.003**
RVEDA	1.02 (0.98–1.06)	0.46	1.07 (1.01–1.14)	**0.02**
RVESA	1.01 (0.96–1.07)	0.73	1.08 (0.99–1.17)	0.06
RVFAC	1.01 (0.97–1.06)	0.67	0.99 (0.93–1.07)	0.84
SPAP	0.99 (0.98–1.01)	0.32	1.00 (0.98–1.03)	0.92
PVR	0.94 (0.65–1.35)	0.73	1.08 (0.63–1.84)	0.78
LV strain	1.01 (0.91–1.12)	0.85	1.03 (0.88–1.21)	0.85
RV strain	0.96 (0.89–1.02)	0.16	1.05 (0.94–1.18)	0.38
After transplantation				
LVEDV	1.00 (0.98–1.07)	0.47	1.00 (0.93–1.08)	0.15
LVSV	1.00 (0.97–1.02)	0.49	0.99 (0.94–1.00)	0.07
LVEF	1.00 (0.97–1.04)	0.85	0.98 (0.93–1.05)	0.62
LA volume	1.00 (0.98–1.02)	0.61	1.00 (0.96–1.03)	0.46
E/A	0.94 (0.61–1.43)	0.76	0.93 (0.48–1.80)	0.83
E/e′	1.09 (0.98–1.20)	0.11	1.05 (0.89–1.24)	0.11
RVEDA	1.07 (1.00–1.14)	**0.05**	1.04 (0.93–1.17)	0.47
RVESA	1.01 (0.99–1.21)	0.07	1.06 (0.90–1.25)	0.51
RVFAC	0.99 (0.94–1.05)	0.71	1.00 (0.91–1.08)	0.89
SPAP	1.04 (1.02–1.06)	**<0.001**	1.05 (1.02–1.09)	**0.004**
PVR	1.76 (0.99–3.14)	0.06	2.56 (1.08–6.15)	0.03
LV strain	1.13 (1.02–1.25)	**0.017**	1.11 (0.94–1.32)	0.22
RV strain	1.15 (1.06–1.26)	**0.001**	1.24 (1.06–1.46)	**0.01**

The hazard ratio for a 1-U increase in the predictor (e.g., ml, %, and mm Hg). **Bold** indicates p ≤ 0.05.

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 2.

improvement of PHT (SPAP). Post-LTx impaired RV strain and increased SPAP were independent predictors of all-cause death. Post-transplantation RV function may provide important prognostic data in patients with LTx. Pre-transplantation RV parameters, however, did not predict outcome, suggesting that increased SPAP and reduced RV function may not discourage clinicians from considering LTx. However, our study is based on a highly and retrospectively selected group, as these patients were selected as suitable candidates for transplantation and also survived to undergo post-transplantation echocardiography; therefore, larger prospective studies are needed to verify the benefit of pre- and post-transplantation RV function in this cohort.

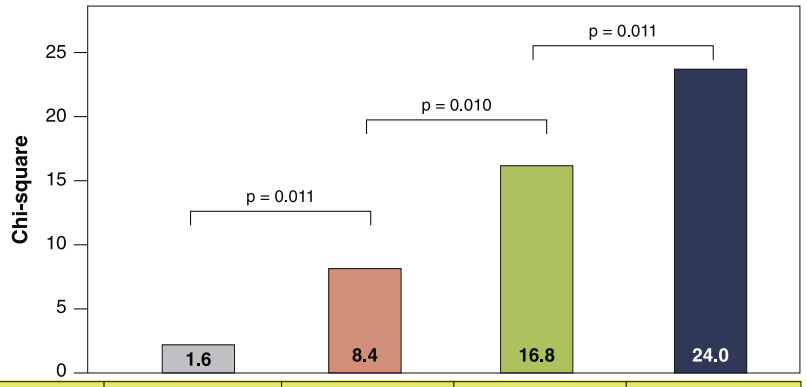
CARDIAC FUNCTION IN LTX. Severe pulmonary disease affects the right and left ventricles, pulmonary vascular bed, and venous return. It also leads to increased expiratory pressures in the thoracic cavity and to a decrease in stroke volume and cardiac output (20). In our study, post-LTx echocardiographic examinations showed that stroke volume increased and RV size, function, and SPAP normalized, which resulted in a reverse remodeling of the distorted cardiac geometry, especially in higher PAP before transplantation. In addition, RV strain as a sensitive marker of RV function also improved after LTx. Although the etiology of these changes is likely multifactorial, one likely contributing factor is diminished PAP (RV afterload), with associated normalization of RV size and function. These results are consistent with those of previous work that showed normalization of SPAP and RV geometry after LTx (8,9). Interestingly, E/A and E/e′, markers of LV filling pressure, increased after LTx. The cause of LV dysfunction in pulmonary disease is not fully understood given the complex interaction between cardiac and pulmonary physiology (21). One possible explanation is that venous return normalized after LTx and led to increased LV pre-load in a setting of pre-clinical LV dysfunction.

TABLE 5 Cox Proportional-Hazards Regression Analysis for the Prediction of All-Cause Death in Multivariate Model

	HR (95% CI)	p Value
Model 1 with LV variables	Chi-square = 10.2	
Age	0.97 (0.89–1.05)	0.45
Male	0.57 (0.21–1.58)	0.28
Double transplantation	1.31 (0.43–4.00)	0.64
Pulmonary fibrosis	1.45 (0.47–4.47)	0.52
E/e′ at baseline	1.16 (0.99–1.35)	0.07
LV strain after transplantation	1.23 (1.00–1.52)	**0.05**
Model 2 with RV variables	Chi-square = 23.8	
Age	1.03 (0.98–1.08)	0.21
Male	1.15 (0.59–2.23)	0.68
Double transplantation	1.43 (0.75–2.77)	0.29
Pulmonary fibrosis	0.93 (0.50–1.71)	0.80
SPAP after transplantation	1.03 (1.01–1.05)	**0.011**
RV strain after transplantation	1.13 (1.04–1.23)	**0.005**
Model 3 after adjustment of time interval of post-Tx	Chi-square = 25.7	
Age	1.02 (0.96–1.07)	0.59
Male	1.26 (0.65–2.44)	0.49
Double transplantation	0.89 (0.45–1.77)	0.73
Pulmonary fibrosis	0.92 (0.49–1.72)	0.79
Time interval after surgery (per month)	0.99 (0.97–1.01)	0.31
SPAP after transplantation	1.03 (1.01–1.06)	**0.023**
RV strain after transplantation	1.16 (1.07–1.26)	**0.001**

The hazard ratio for a 1-U increase in the predictor (e.g., ml, %, and mm Hg). **Bold** indicates p ≤ 0.05.

Tx = transplant; other abbreviations as in Tables 2 and 4.



	Clinical Data	+ LV Strain	+ SPAP	+ RV Strain
Age	1.03 (0.98-1.08) p = 0.26	1.02 (0.98-1.07) p = 0.32	1.02 (0.98-1.07) p = 0.36	1.03 (0.98-1.08) p = 0.21
Male Sex	0.89 (0.48-1.64) p = 0.70	0.76 (0.41-1.44) p = 0.41	1.04 (0.52-2.05) p = 0.92	1.08 (0.54-2.15) p = 0.83
Double Transplantaion	1.04 (0.56-1.95) p = 0.89	1.00 (0.53-1.89) p = 0.99	1.21 (0.62-2.34) p = 0.57	1.37 (0.70-2.69) p = 0.36
Idiopathic Pulmonary Fibrosis	1.16 (0.64-2.11) p = 0.62	1.39 (0.76-2.56) p = 0.29	1.12 (0.59-2.13) p = 0.72	0.99 (0.52-1.89) p = 0.98
LV Strain		1.15 (1.03-1.27) p = 0.01	1.09 (0.98-1.22) p = 0.11	1.04 (0.93-1.16) p = 0.53
sPAP			1.04 (1.01-1.06) p = 0.005	1.03 (1.01-1.05) p = 0.024
RV Strain				1.12 (1.02-1.23) p = 0.015

FIGURE 3 Incremental Prognostic Value of Echocardiographic Parameters When Added to Clinical Data

Illustration of the change in global chi-square of sequential Cox models incorporating clinical (age, sex, surgery type, and lung disease etiology), left ventricular (LV) function (global LV strain), pulmonary hypertension (systolic pulmonary artery pressure [SPAP]), and right ventricular (RV) function (RV strain).

PREDICTORS OF MORTALITY IN LTX. There is increasing recognition of the prognostic information provided by RV function in cardiovascular disorders such as heart failure and PHT (22). Moreover, quantitative measurement of RV size and function is important in the prediction of clinical outcomes in several disease states (6,14). In LTx patients, pre-LTx SPAP has also been shown to be associated with mortality, based on an analysis from the registry of the International Society for Heart and Lung Transplantation. However, there was no association between pre-LTx SPAP and clinical outcome shown on multivariable analysis (3). In listing the criteria of LTx, pre-LTx increased SPAP was not included (23). Our findings are consistent with those of previously published work. In addition, pre-LTx RV echocardiographic parameters are strongly influenced by the afterload status (lung status) (24). As shown in our results, RV parameters improved after LTx and may provide a valuable tool to assess prognosis. We also evaluated the contribution of RV systolic function and SPAP. Especially in the post-LTx population, many echocardiographic RV parameters were found to be within normal range. This suggests that more sensitive markers are required to detect subclinical RV dysfunction. Several investigators have suggested that RV strain can detect cardiac dysfunction earlier than standard imaging parameters and is associated with clinical outcomes (6,7,14). Our findings support the advantage of RV strain in the early detection of RV dysfunction. Therefore, the combination of impaired RV strain and increased SPAP may provide incremental predictive value for the prognosis of LTx patients. Previous studies also suggested that several clinical features were associated with mortality after LTx. Our institution has shown that survival is worse after LTx for idiopathic pulmonary fibrosis and when single LTx is performed than for other clinical scenarios of LTx (17). Therefore, we incorporated the etiology of pre-existing disease and the type of surgery performed into the final model. However, in the present study, neither

of these factors was significantly associated with mortality after LTx. A possible explanation for this is the relatively small sample size in the current investigation. Therefore, our findings may not be extrapolated to all patients after LTx.

STUDY LIMITATIONS. This was a single-center study that included a select population of LTx patients including only those with follow-up echocardiographic studies and was not a prospective study. Further prospective study with a large study population is required to elucidate that post-transplantation RV function can risk-stratify patients after LTx. In addition, we could not enter some pertinent clinical variables (for example, donor status) due to the relatively small sample size, which poses a potential risk of model overfit. With the cardiac death model, there is the potential of over fitting due to censoring of the cases with noncardiac death (25). The present study should be considered as hypothesis generating, and we believe that larger multicenter studies are warranted. Moreover, there was considerable variation in the time to post-operative echocardiography in this study, and this may have affected our ability to detect improvement in subclinical cardiac dysfunction after LTx. Additionally, because post-LTx patients only undergo echocardiography in the setting of cardiac history or clinical indication, referral bias may be present in our study. Echocardiographic variables may be late features associated with clinical decline rather than an early predictor of future decline. Velocity vector imaging is vendor-independent strain software that is relatively easy to use, but its clinical utility remains unproven. We were not able to assess the strain rate using strain imaging due to the limited frame rate (26).

CONCLUSIONS

In post-LTx patients, impaired RV strain and increased SPAP were independently associated with all-cause mortality. Alterations of RV function and PAP normalize, and post-transplantation RV function may provide important prognostic data in LTx patients. Incorporating more detailed evaluation of the effects of PHT on cardiac anatomy and function may improve prediction models of outcome in this challenging patient group. Interestingly, pre-transplantation RV parameters did not predict outcome, suggesting that increased SPAP and reduced RV function may not discourage clinicians from considering LTx. Our study is based on a highly and retrospectively selected group. We believe that larger prospective studies are warranted to confirm this result.

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APPENDIX For a supplemental video and figures, please see the online version of this article.

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