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Clinical and echocardiographic predictors of outcome in liver transplant patients

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Abstract

Liver transplant (LT) candidates undergo transthoracic echocardiography (TTE) before surgery to assess cardiac function and evaluate the echocardiographic probability of pulmonary hypertension (PHT). The improvement of pulmonary artery systolic pressure (PASP) after transplant is associated with higher survival rates in patients with mild or moderate PHT. Although studies analyze the outcomes of LT in patients treated for PHT, the prognostic value of PASP in patients without PHT in the follow-up is unknown. The aim of our study is to evaluate pre- and post-LT cardiac function, right ventricular function, pulmonary artery pressure, and their association with long-term mortality. 102 patients who underwent LT between 2011 and 2018 were compared for echocardiographic and hemodynamic parameters pre- and post-LT. After LT, systolic blood pressure, heart rate (HR), and PASP significantly increased, while tricuspid annular plane systolic excursion/PASP decreased. Moreover, the higher difference in HR and PASP between pre- and post-LT was highlighted in those patients who died during the follow-up period after LT. Among all the parameters tested, in the multi-variable Cox regression for mortality, left ventricular ejection fraction and PASP difference were predictors of mortality. This study highlights the importance of TTE in LT screening as a tool to stratify patients at higher risk of death due to advanced cirrhotic cardiomyopathy and the importance of the change of echocardiographic parameters, in particular right and left ventricular hemodynamics, during the follow-up period. These parameters could be used to guide a more aggressive therapy.

Key words: liver transplant, heart function, liver cirrhosis, right ventricular dysfunction.

Introduction

Cirrhosis-related cardiovascular abnormalities include decreased peripheral vascular resistance, decreased mean arterial pressure, and increased cardiac output. Because of peripheral vasodilation, cardiac output (CO) at rest is normal or increased. Nevertheless, echocardiography may reveal some abnormal diastolic and systolic parameters, a condition called "cirrhotic cardiomyopathy" [1]. An inflammatory phenotype characterizes the pathogenesis: endotoxemia stimulates cytokines and cardiodepressant mediators such as nitric

oxide and endocannabinoids. In addition, cardiac dysfunction contributes to the pathogenesis of hepatorenal syndrome and increases cirrhotic patients' morbidity and mortality due to hemorrhage, infection, surgery, and liver transplantation (LT). Cirrhotic cardiomyopathy, manifesting as inadequate cardiac responsiveness to these challenges, underlies an increased fragility in end-stage liver patients, impacting the clinical course and outcomes during and after LT. Therefore, LT candidates typically undergo comprehensive transthoracic echocardiography (TTE) as part of the preoperative transplant work-up to assess cardiac function and to evaluate the echocardiographic probability of pulmonary hypertension [2]. Notably, a mean pulmonary artery pressure (mPAP) of >50 mmHg at the time of liver transplantation had 100% perioperative mortality [3]. The improvement of systolic pulmonary artery pressure values after transplant surgery is associated with higher survival rates in patients with mild or moderate pulmonary hypertension (PHT). Although many studies analyse the outcomes of LT in patients treated for PHT with a mPAP \geq 35 mmHg, the prognostic value of systolic pulmonary pressure in patients without PHT in the long term follow-up is unknown.

The aim of our study is to evaluate pre and post – liver transplant cardiac function, in particular right ventricular function and pulmonary artery pressure and their association with long term mortality.

Materials and Methods

Study population. 102 patients who underwent LT between January 2011 and December 2018 and performed a pre- and post- LT transthoracic echocardiogram (TTE) at least 6 months after surgery at King Faisal Specialist Hospital and Research Centre, Riyadh, KSA, were retrospectively identified. Exclusion criteria included patients who had low quality TTE, missing pre or post TEE and age younger than 18 years old.

All the candidates received a complete evaluation according to the standard protocol of the Hospital including complete history and comorbidities, physical examination (weight, systolic and diastolic blood pressure [SBP and DBP]), blood analysis (red blood cell count, biochemistry and coagulation parameters).

Demographic, clinical data and outcome were collected from medical records. The main follow-up outcome measure was overall survival. Death occurrence and date were extracted from medical records when available. The overall survival was the main measure of mortality. The study was approved by the local Ethical Committee (REC number 2191217)

Echocardiographic evaluation. All patients underwent complete TTE performed by trained echocardiographers according to the international standards defined by the American Society of Echocardiography (ASE)/ European Association of Cardiovascular Imaging (EACVI) [4,5]. All

examinations were reviewed and analyzed by 3 certified experts in TTE (S.A. and A.A.) with an image processing workstation Excelera and Image Arena version 4.6 software (TomTec Imaging Systems, Unterschleissheim, Germany) for strain analysis (O.V.), blinded for patients' outcome. Each parameter was assessed in three to five consecutive cardiac cycles, and the mean values were used for data recording and analysis. For global longitudinal strain (GLS), endocardial borders were traced on the end-systolic frame in four-, two- and three-chamber view, with end-systole defined by the QRS complex. The software (TomTec Imaging Systems, Unterschleissheim, Germany) tracks speckles along the endocardial border throughout the cardiac cycle. Peak longitudinal strain was computed automatically, generating regional data from six segments and an average value for each view and then a final "Bull Eye" was generated. Echocardiographic images of the right ventricle (RV) focused apical four-chamber view were used for RV myocardial deformation parameters using the same software package mentioned above for GLS. After manual identification of the end-systolic RV endocardial border by three points (two on the tricuspid annulus, and one at the RV apex). We calculated the right ventricular free wall longitudinal strain (RVFWLS) value as recommended in the consensus document issued by the ASE/EACVI/Industry Task Force [6].

Additional measurements of the RV were considered such as the right ventricle basal diameter (RVBD), and right atrial volume (RAV). Right ventricular function was evaluated considering fractional area change (FAC) that was derived as $[(RV \text{ diastolic area} - RV \text{ systolic area}) / RV \text{ diastolic area} * 100]$. Pulsed tissue Doppler imaging (TDI) examination was performed to evaluate the longitudinal myocardial motion, placing a sample volume gate on the tricuspid annulus in the apical four-chamber view. Tricuspid annular plane systolic excursion (TAPSE), a parameter of global RV function which describes apex-to-base shortening, was obtained from apical four-chamber view, placing the M-mode line at the lateral tricuspid valve annulus and measuring the height of the annulus movement during systole (normal values > 17 mm according to the guidelines) [4]. The Continuous wave (CW) Doppler of the tricuspid regurgitation (TR) trace was used to measure the difference in pressures between the right ventricle and right atrium.

The simplified Bernoulli equation ($P = 4[TR_{max}]^2$) is used to calculate pressure difference using peak TR velocity, a value < 2.8 m/s is considered normal. A coaxial TR jet is identified in parasternal long axis (RV inflow), parasternal short axis, or apical four-chamber view. The peak velocity of the envelope is measured (TR_{max}) and the right atrial pressure (RAP) is assumed by the size and distensibility of inferior vena cava (IVC) during inspiration at rest and during forced inhalation, and this value is added to the peak TR velocity [7] to obtain the systolic pulmonary

artery pressure (PASP). Right ventricular arterial coupling was evaluated using RVFWLS, TAPSE/PASP ratio and RVFWLS/PASP ratio [8-10].

Statistical analysis. Variables were expressed as mean and standard deviation (SD). Clinical and TTE characteristics pre- and post-LT were calculated and compared using dependent Student's t-tests for pre- and post-LT. Independent Student's t-test or two-sample Wilcoxon rank-sum test to compare alive and deceased patients for continuous variables with normal distribution and for not normal distributed variables were obtained. Univariate Cox regression analysis was used to select those variables statistically significant to be in the multivariate Cox regression analysis for overall survival. Hazard ratios and corresponding two-sided 95% confidence intervals were derived from the regression coefficients in the Cox models. The threshold of statistical significance was 0.05 for all tests used. Statistical analysis were performed using STATA version 16.

Results

A cohort of 102 patients (61 males, 59.8%, median age 59 years) who performed a TTE before and after LT in our Hospital were identified. The main liver cirrhosis etiology was chronic viral hepatitis C (38,2%), followed by chronic viral hepatitis B (18,6%) (Table 1). The median time between the pre-LT TEE and LT was 51 days, the median time between the LT and the post surgery TEE was 476 days. Follow-up time was 2171 ± 1027 days (mean \pm SD). At the end of the follow-up 76 patients (74.5%) were alive, 16 (15.7%) has died and 10 (9.8%) were lost to follow-up (Table 1). Figure 1 presents the Kaplan-Meier survival curve for the population studied. Hemodynamic parameters pre- and post- LT are reported in Figure 2. Echocardiographic parameters pre-and post-LT are reported in Table 2, Table 3 shows the hemodynamic and echocardiographic differences between alive and deceased patients after liver transplant (LT). Left ventricular mass index, and relative wall thickness (RWT) increased but the difference was not significant. Stroke volume (SV), cardiac output (CO), and E/A ratio, did not change significantly. Left ventricular ejection fraction (LVEF) decreased but the difference was of borderline significant. PAPS increased significantly after LT while TAPSE, right S' on TDI, longitudinal strain of the RV, TAPSE/PASP, and RVFWLS/PASP did not change significantly.

In uni-variable Cox regression analysis for mortality, hemodynamic parameters, cardiovascular risk factors and echocardiographic parameters were tested. The statistically significant variables obtained were tested in the multi-variable Cox regression analysis for mortality (Table 4). The increase in LVEF and PAPS, expressed as the difference between post and pre LT values, were associated with death.

Discussion

The main findings of our study are: 1) all the hemodynamic parameters increased after LT, in particular SBP and HR, 2) a higher difference of HR between pre- and post-LT was highlighted in patients who did not survive, 3) there was a mild but significant increase in PASP after LT, although within the normal range, but in those who died the increase was above the limit of normality and, 4) the parameters that were significantly and independently associated with mortality were PASP and pre- and post LVEF difference.

The present data supported the prognostic role of right ventricular afterload in end-stage liver disease patients with right ventricular function and pulmonary pressure values within the normal limits before transplantation. End-stage liver disease is characterized by vascular changes such as splanchnic vasodilatation and increased blood flow leading to hyperdynamic circulation and a slight increase in pulmonary pressures [11]. In addition, splanchnic collaterals caused smooth muscle hypertrophy and remodeling of the pulmonary vasculature, leading to porto-pulmonary hypertension [12]. This hemodynamic state coexists with LV systolic and diastolic dysfunction, a condition called cirrhotic cardiomyopathy. The Cirrhotic Cardiomyopathy Consortium, established in 2018, revised the diagnostic criteria for cirrhotic cardiomyopathy following novel concepts and methods that have emerged in echocardiography over the last 15 years [13]. The proposed criteria rely on cardiac abnormalities identified by advanced ultrasonography, such as tissue Doppler imaging and two-dimensional speckle-tracking echocardiography. When examined by 2-dimensional speckle-tracking echocardiography, patients with cirrhotic cardiomyopathy can show reduction in global longitudinal strain (GLS) $< 18\%$ or LVEF $< 50\%$ on 2D echocardiography. Compared to systolic dysfunction, diastolic dysfunction is more common in this pathology, based on the new diagnostic criteria which considers diastolic dysfunction when 3 of the following parameters are present: septal e' velocity < 7 cm/s, E/e' ratio > 15 , LAVI > 34 mL/m², TR velocity > 2.8 m/s. In our study, LT candidates had normal pre- and post-LT EF and diastolic function parameters within the normal range or mildly abnormal, included the right heart function and PASP. Our data show that after transplantation, the hyperdynamic state improves as demonstrated by parameters such as LVEF, RV FAC, TAPSE, and right ventricular systolic and diastolic area. On the other hand, a significant increase in PASP occurs following surgery in particular in those who died. The LVEF or did not change between pre- and post- transplant or increased in those who died. This observation may be explained by the fact that, even in cases where the hyperdynamic state has been resolved, a subset of patients continues to have both the LV hyperdynamic state and a negative pulmonary artery remodelling. At the time of transplantation, the clinical state associated with liver dysfunction in these patients was no

longer reversible, and in the follow-up, it became a predictive factor for mortality. The results highlighted that even in the case of pulmonary pressure values within the normal limits or mildly increased, the non-invasive evaluation of PASP and EF by TTE can be a sensitive parameter to assess which patients are at greater risk of negative outcomes after transplantation. A similar concept is expressed by increased heart rate. Increased resting HR due to hyperdynamic circulation is associated with all-cause mortality in LT recipients, as reported by Kwon et al. [14], demonstrating that patients with HR >80 beats/min had a significantly higher risk of death compared to patients with HR ≤65 beats/min. Right ventricular–pulmonary artery coupling (RV-PA coupling) refers to the relationship between RV contractility and RV afterload. A lower ratio indicates an inadequate RV contractile response to afterload variations. In this study two parameters of RV-PA were used (TAPSE/PAPS, RVFWLS/PASP) but none of them were able to discriminate those who survived from those who died. Most likely, in this particular population the increase in PASP and its predictivity for mortality, includes other settings and the RV function maintained a good adaptation to increase in PASP. More frequent echocardiographic monitoring may be offered in patients with normal estimated lung pressures with higher differences between pre- and post- LT of PASP and LVEF values and higher values after surgery might identify patients at higher risk of dying due to poor hemodynamic and circulatory adaptation.

This study had several limitations. First, it used a retrospective design in which no additional detailed workup has been performed to identify other causes of PHT. Second, patients did not undergo right-heart catheterization. Instead, PAPS was determined noninvasively using Doppler echocardiography and considering the inaccuracies in RAP estimation, the latest ESC Pulmonary Hypertension Guidelines recommend the use of peak TRV instead the estimated PAP as the variable for assigning the echocardiographic probability of PHT [15]. Catheterization may have elicited more accurate and additional data about pulmonary hemodynamics, such as pulmonary vascular resistance and cardiac output. However, in most trials, PAPS was obtained using Doppler echo-cardiography by the method used in our study as the new guidelines have been published recently.

Conclusions

In conclusion, our data shows that 1) SBP and HR were higher after LT as well as PASP, although within normal limits. 2) In those patients who died after LT, PASP was significantly higher. This study highlights the importance of pre- and post-LT TTE screening as a tool to stratify patients at higher risk of death due to more advanced cirrhotic cardiomyopathy indicated by increased PAPS and change in EF. These parameters could be used to guide a more aggressive therapy.

More studies are required in light of new guidelines to assess the risk of increased pulmonary pressure and confirm the role of TTE as a non-invasive component essential for monitoring the risk of death in LT recipients.

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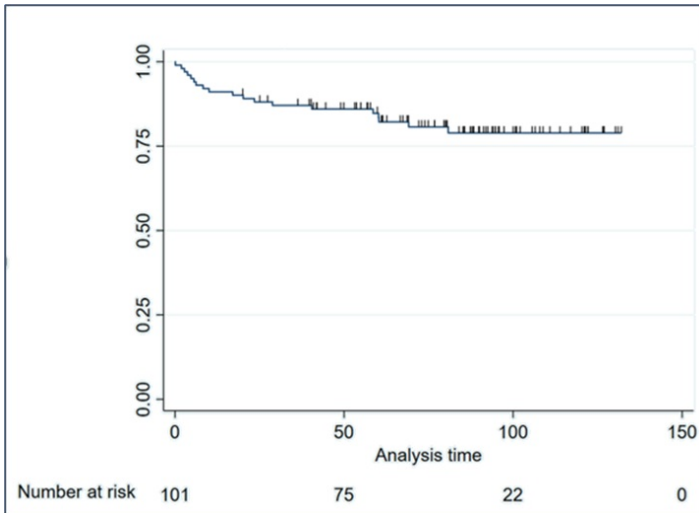


Figure 1. The Kaplan-Meier survival curve of the liver transplant population studied.

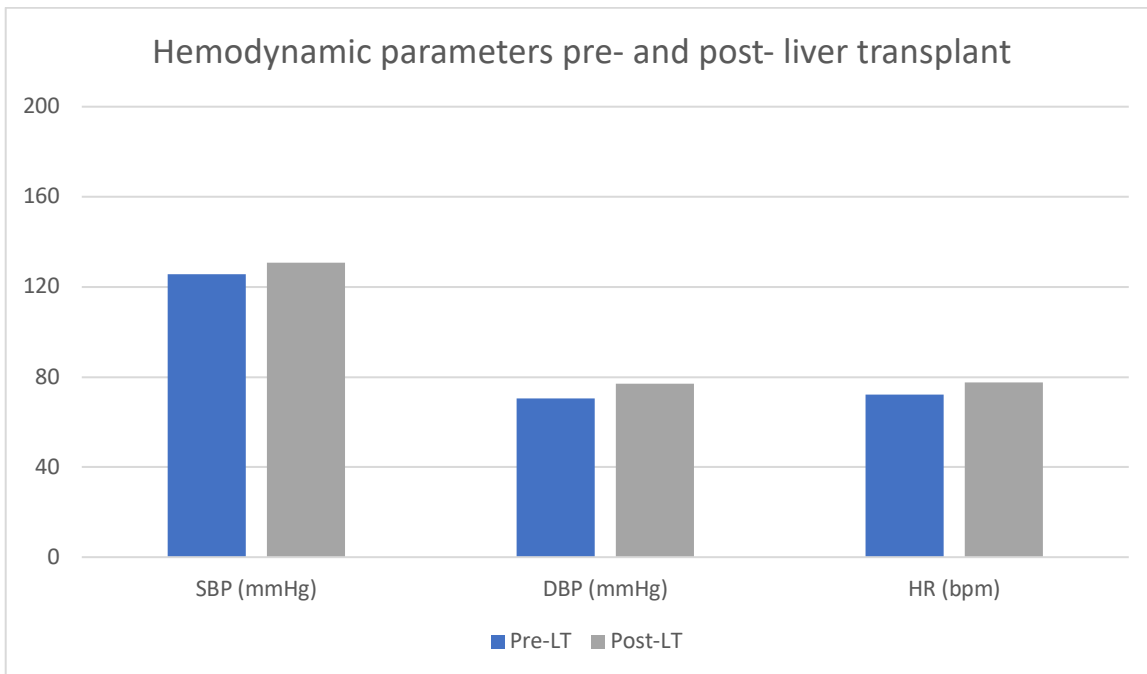


Figure 2. Hemodynamic parameters pre- and post-liver transplant. LT, liver transplant; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

Table 1. Baseline characteristics of the liver transplant population studied.

Age, years (median)	59 (54-65)
BMI (median) Kg/m²	28.63 (24.69-31.57)
BSA (median) m²	1.77 (1.61-1.90)
Comorbidities	Hypertension 35 (24.6%) Diabetes 67 (66.2%) CAD 11 (10.9%)
Indication to LT	Chronic viral hepatitis C 39 (38.2%) Chronic viral hepatitis B 19 (18.6%) Autoimmune hepatitis 13 (12.7%) Cryptogenic liver cirrhosis 12 (11.8%) Non-alcoholic steatohepatitis 12 (11.8%) Schistosomiasis (Bilharziasis) 3 Primary biliary cirrhosis 2 Primary Sclerosing Cholangitis 1 Liver infarction 1
Therapy at baseline evaluation	Betablockers 49 (48.5%) Aspirin 26 (25.5%) ACE-I 17 (16.8%) ARB 9 (8.8%) Furosemide 79 (78.2%) Spironolactone 65 (64.4%)
Days between TTE and LT	51 (26-161)
Days between LT and follow-up TTE	476 (133-880)
Patients alive at the end of follow-up	76 (74.5%)
Patients died at the end of follow-up	16 (15.7%)
Patients lost at the follow-up	10 (9,8%)

Continuous variables are reported as median, and categorical variables are described as number of subjects (%). BMI, body mass index; BSA, body surface area; CAD, coronary artery disease; INR, international normalized ratio; ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; TTE, transthoracic echocardiography.

Table 2. Echocardiographic parameters pre- and post-liver transplant.

Variables	Pre-LT (mean ± SD)	Post-LT (mean ± SD)	P value
<i>Left ventricle</i>			
LVM index (g/m ²)	78.93±18.8	90.09±31.3	0.53
RWT	33.2±6.52	37.6±8.5	0.47
LVEF (%)	62.12±7.2	57.1±9.20	0.056
CO (mL/min)	5447.6±1714.14	5184.8± 1525	0.32
E/A	1.23±0.57	0.94±0.62	0.63
E/Em lat	7.68±3.32	8.66±3.63	0.39
LVGLS (%)	- 21.5±4.17	- 17.57±3.62	0.89
<i>Right ventricle</i>			
RVDA (cm ²)	17.81±6.2	15.49±4	0.04
RVSA (cm ²)	8.47±2.49	7.98±2.47	0.09
RV FAC (%)	51.70±7.6	48.31±8.7	0.52
TAPSE (mm)	24.37±4.8	21.01±3.5	0.56
PAPS (mmHg)	26.90±7.9	28.04±13.3	0.011
TAPSE/PASP	0.98±0.35	0.91±0.47	0.01
RVFWLS (%)	-24.82±9.0	-21.37±8.2	0.82
RVFWLS/PASP	-0.98±0.52	-0.87±0.53	0.12
S'(mm)	14.16±2.7	12.34±2.7	0.65

Left and right side morphological and functional features. P value is calculated for the difference between pre-transplant and post-transplant value. LVM, left ventricular mass; RWT, relative wall thickness; LVEF, left ventricular ejection fraction; SV, stroke volume; CO, cardiac output; LVGLS, left ventricular global longitudinal strain; E, early diastolic transmitral flow velocity; A, late (atrial) diastolic transmitral flow velocity; Em lat, early diastolic mitral annulus lateral velocity; RVDA, Right ventricle diastolic area; RVSA, Right ventricle systolic area; FAC, Fractional Area Change; TAPSE, tricuspid annular plane excursion; PAPS, Pulmonary artery systolic pressure; RVFWLS, Right ventricle free wall longitudinal strain; S', Tissue Doppler imaging (TDI)-derived tricuspid lateral annular systolic velocity.

Table 3. Two-sample Wilcoxon rank-sum test to compare hemodynamic and echocardiographic features between alive and dead population after liver transplant.

	Pre-LT		p-value	Post- LT		p-value	Difference		p-value
	Alive	Dead		Alive	Dead		Alive	Dead	
SBP (mmHg)	125.19±1 6	126.73±2 0	0.88	131.0±1 8	130.36±2 1	0.73	5.6±16	3.6±20	0.3
DBP (mmHg)	71.68 ±11	63 ±13	0.013	74.17±1 1	64.89±13	0.008	2.2±11	1.8±20	0.92
HR (bpm)	73.78±17	65.10±9	0.046	77.16±1 3	78.89±23	0.231	4.1±16	14.8±27	0.03
Creatinine (mL/min)	92.77±51	111±121	0.67	8.44±7. 2	7.31±2.1	0.74	-84±51	-108±12	0.97
LVEF(%)	62.21±7. 5	61.70±5. 5	0.62	56.25±8	61.02±9. 5	0.056	- 5.9±10	- 0.68±12	0.056
TAPSE (mm)	24±4.59	25.9±5.3	0.32	20.78±3	22.03±3	0.27	- 3.3±4.9	- 4.2±6.5	0.56
PAPS (mmHg)	26.85±2. 2	27.13±5. 6	0.67	26.07±9	36.33±9	0.016	-0.98±1	10.6±2	0.011
RVFWLS (%)	- 24.79±9. 3	- 24.93±7. 5	0.92	- 21.28±8	-21.78±6	0.12	3.28±1	3.14±7	0.82
TAPSE/ PASP	0.98±0.3 7	0.99±0.2 7	0.47	0.92±0. 4	0.86±0.5	0.49	-0.03±4	- 0.2±0.5	0.5
RVFWLS/P APS	- 0.9±0.54 1	- 1.01±0.4 8	0.85	-0.09±5	-0.77±4	0.120	0.06±6	0.23±7	0.82

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LVEF, left ventricular ejection fraction; TAPSE, tricuspid annular plane excursion; PAPS, pulmonary artery systolic pressure; RVFWLS, right ventricle free wall longitudinal strain. Difference is the post-transplant value minus the pre-transplant value.

Table 4. Multi-variable Cox regression for mortality in liver transplant.

Variable	Hazard Ratio	p-value	CI
DPB pre-LT	0.950	0.052	0.902-1.000
HR pre-LT	0.967	0.174	0.922-1.014
HR difference*	1.022	0.260	0.983-1.062
BMI pre-LT	0.912	0.079	0.824-1.010
LVEF difference*	1.058	0.028	1.006-1.114
PASP difference*	1.042	0.014	1.000-1.078

DBP, diastolic blood pressure; HR, heart rate; BMI, body mass index; LVEF, left ventricular ejection fraction; PASP, Pulmonary artery systolic pressure; *difference is the post-transplant value minus the pre-transplant value.