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Research Article

Mildly Elevated Pulmonary Artery Systolic Pressure is Associated with Extracorporeal Membrane Oxygenation Support after Heart Transplantation

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Background. Pulmonary hypertension is a well-known risk factor for hemodynamic instability after heart transplantation. However, it remains unclear whether a mild elevation of pulmonary artery systolic pressure (PASP) is associated with higher risks of graft dysfunction and resultant extracorporeal membrane oxygenation (ECMO) support. *Methods*. From 2016 to 2021, 102 adult recipients undergoing orthotopic heart transplantation at our institution were investigated (mean age, 48.5 ± 13.2 years; 22.5% female). This study cohort was stratified into 3 groups based on the PASP measured by right heart catheterization before surgery: >50 mmHg, 35–50 mmHg, and <35 mmHg. The primary end point was ECMO support after procedure. *Results*. ECMO was implemented in 24 (23.5%) patients due to difficult weaning from cardiopulmonary bypass or cardiac low output in the intensive care unit, which was likely to be associated with higher mortality ($P = 0.053$). Age, gender, comorbidities, preoperative medications, and graft ischemia time were comparable across the 3 groups. The use of ECMO was significantly more common in patients with baseline PASP >50 mmHg (11/36, 30.6%) and 35–50 mmHg (12/38, 31.6%), while only 1 (3.6%) patient with baseline PASP <35 mmHg required ECMO support after transplant ($P = 0.007$). Multivariate logistic models demonstrated that PASP (odds ratio = 2.34; $P = 0.028$) and cardiopulmonary bypass time (odds ratio = 1.01; $P < 0.001$) were independent risk factors for postoperative ECMO. *Conclusions*. A mild elevation of pretransplant PASP (e.g., 35–50 mmHg) is related to low cardiac output and subsequent ECMO after heart transplantation, for which prompt administration of vasodilators before transplant may be protective.

1. Introduction

Heart transplantation (HTx) is the definitive treatment for patients with advanced heart failure who have evidence of poor prognosis and limited symptoms despite optimal conventional therapy [1]. The most common cause of in-hospital mortality after HTx is graft dysfunction [2], which also influences late survival [3]. Extracorporeal membrane oxygenation (ECMO) has been widely adopted in HTx recipients with severe graft dysfunction and difficulty in weaning from cardiopulmonary bypass (CPB) [4, 5]. Pretransplant pulmonary hypertension is a known risk factor for cardiac graft dysfunction, and the current guidelines recommend vasodilator challenge and other medical treatments in HTx candidates with a pulmonary artery systolic pressure (PASP) ≥50 mmHg [6]. Recently, several studies showed that even mild elevation of pulmonary artery pressure was associated with higher mortality in the general population [7, 8], while the impact of a lower PASP, e.g., PASP 35–50 mmHg, on the risk of ECMO support following HTx remains less studied.

In this study, we aimed to study the relationship between pretransplant PASP and ECMO after HTx. We hypothesized that ECMO use was similarly common in recipients with mild elevation of PASP and in those with evident pulmonary hypertension.

2. Methods

2.1. Study Population. From January, 2016, to March, 2021, all patients who underwent HTx at the Department of Cardiac Surgery, Zhongshan Hospital Fudan University, were investigated. Our institutional criteria for HTx were based on the 2016 ISHLT listing criteria for heart transplantation [6], and recipient assessment and management were conducted as recommended. Patients with fixed, primary pulmonary hypertension and the Eisenmenger syndrome were excluded from HTx. For patients with escalating pulmonary artery pressure due to left heart failure, as determined by right heart catheterization or echocardiography data, enhanced diuretic therapy (tolvaptan and recombinant human brain natriuretic peptide) and inotropes (catecholamines, milrinone, and levosimendan) were administered in addition to the guideline-directed medical therapies. In this study, we excluded patients (1) aged < 18 years, (2) undergoing retransplantation, and (3) with missing right heart catheterization data. This study has been approved by the Zhongshan Hospital Ethics Committee (approval number: B2021-668R). All organ donors and recipients have signed an informed consent form for biomedical research.

In 2015, China enacted a law prohibiting executed criminal donor organs, and the China Organ Transplant Response System was started in the same year. The rule of donor-recipient size matching in the current organ sharing system is based on the threshold of ±20% of the recipient's weight, which does not include right heart parameters such as PASP. Organ allocation is automatically completed in the system, and surgeons cannot manually screen donors. No "marginal" or "alternative" types of donors were listed in the system and thereby not used. In this study, we included HTx recipients operated from 2016 to 2021, which precluded the possibility of executed donor organ utilization. The follow-up time was limited to 180 days postoperatively due to the retrospective nature of this study.

2.2. Measurement of PASP. PASP was measured by right heart catheterization using a balloon-tipped Swan–Ganz thermodilution catheter through the right internal jugular vein. In this study, all right heart catheterization data were collected within 6 months prior to HTx, when patients already received titrated medical therapy including loop diuretics, aldosterone receptor antagonists, beta-blockers, digoxin, angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARBs), and angiotensin receptor-neprilysin inhibitors. Intravenous inotropic agents and levosimendan were administered as appropriate. Vasodilator challenge was performed using intravenous milrinone in candidates with PASP ≥50 mmHg and pulmonary vascular resistance (PVR) ≥3 Wood units, as recommended in the guidelines [6]. Reduction of mean pulmonary artery pressure ≥10 mmHg to reach an absolute value of mean pulmonary artery pressure <40 mmHg was considered responsive to vasodilation [9]. We inserted a pulmonary artery catheter to monitor the pulmonary circulation and guide inotrope/vasodilation therapy during HTx operation. After transplant, the catheter was not used in most cases and usually removed with 5 days.

2.3. Posttransplant ECMO. At our institution, all HTx operations were performed in an orthotopic fashion. After all anastomosis was complete, the contraction of graft ventricles was examined by the operating surgeon and transesophageal echocardiography. For grafts that exhibited impaired contraction, CPB was properly prolonged, and inotropic and vasoactive agents were administered to maintain an acceptable hemodynamic state. A dilated, rigid ventricle, persistent hypotension, elevated central venous pressure, and unchanged pulmonary artery wedge pressure were signs of right ventricular graft dysfunction. In the settings of persistent graft dysfunction that caused difficulty in weaning from CPB, we considered venoarterial ECMO cannulation through femoral access. In the intensive care unit, ECMO weaning was evaluated daily to examine if the patient showed improvement in graft function and peripheral perfusion. In this study cohort, weaning was successful for all suitable patients and no patient required reinsertion of mechanical circulatory support.

2.4. Statistical Analysis. Continuous variables are shown as the means ± standard deviations, and categorical variables are expressed as numbers with percentages. For differences across groups, the one-way analysis of variance was adopted to compare continuous variables, and the chi-square test was used to compare categorical variables. The Kaplan–Meier method was used to estimate postoperative survival from lifetime data, which was adjusted using the inverse probability weighting method (Package "ipw," ver. 1.0–11). The independent risk factors for the use of ECMO were selected by univariate logistic regression, and variables with $P < 0.10$ were entered into multivariate logistic regression with a stepwise selection method. C-statistics (area under the receiver operating characteristic curve) were used to test the discrimination of the model, and goodness-of-fit was assessed using the Hosmer–Lemeshow test. All statistical tests were 2-sided, and $P < 0.05$ was considered statistically significant. Statistical analysis was performed with SPSS 20.0 (SPSS Inc., USA) and R 3.3.3 (R Foundation, Austria).

3. Results

3.1. Recipient Demographics. A total of 102 patients received HTx at Zhongshan Hospital from 2016 to 2021. The age of the patients ranged from 19 years to 72 years (mean age 48.5 ± 13.2 years; median, 52 years), and 23 (22.5%) patients were female. Indications for HTx included dilated cardiomyopathy ($n = 72$), ischemic cardiomyopathy ($n = 9$), restrictive cardiomyopathy ($n = 5$), left ventricular noncompaction ($n = 5$), primary cardiac tumor ($n = 3$),

Table 1: Characteristics of HTx recipients stratified by preoperative PASP.

Demographics	PASP < 35 mmHg $n = 28$	PASP 35–50 mmHg $n = 38$	PASP > 50 mmHg $n = 36$	P value
Age (years)	49.4 ± 15.3	50.5 ± 11.3	45.3 ± 9.7	0.64
Body mass index (kg/m^2)	22.2 ± 3.8	23.9 ± 3.7	21.6 ± 3.4	0.087
Female (%)	7 (25)	9 (23.7)	7 (19.4)	0.87
Prior cardiac surgery (%)	4 (14.3)	8 (21.1)	3 (8.3)	0.32
Ischemic time (min)	232.8 ± 95.7	212.4 ± 115.4	246.8 ± 105.0	0.42
Preoperative				
Brain natriuretic peptide (ng/L)	3460.6 ± 3896.5	4524.4 ± 3862.7	6243.7 ± 6686.2	0.056
Cardiac troponin T (μg/L)	0.2 ± 0.6	0.1 ± 0.1	0.2 ± 0.3	0.14
Total cholesterol (mmol/l)	29.4 ± 22.2	23.9 ± 26.5	25.8 ± 12.4	0.21
Albumin (g/L)	41.7 ± 7.2	41.7 ± 7.2	41.1 ± 7.4	0.33
Alanine aminotransferase (IU/L)	22.3 ± 10.3	71.5 ± 99.8	27 ± 26.3	0.7
Aspartate aminotransferase (IU/L)	61.8 ± 88.4	59.8 ± 84.9	69.4 ± 99.5	0.062
Lactate dehydrogenase (U/L)	297.5 ± 160.3	234 ± 104.9	293.3 ± 110.3	0.3
Glomerular filtration rate (ml/min)	78.8 ± 31.8	75.5 ± 30.1	73.1 ± 28.5	0.73
Serum creatinine (μmoI/L)	122.8 ± 85.1	111.3 ± 54.2	140.0 ± 136.7	0.6
Left ventricular end-diastolic dimension (mm)	61.3 ± 14.9	67.1 ± 13.8	67.5 ± 14.7	0.084
Left ventricular ejection fraction (%)	36.2 ± 15.8	31.8 ± 14.9	27.5 ± 10.8	0.18
Cardiac output (L/min)	3.8 ± 0.8	3.3 ± 1.5	3.5 ± 1.3	0.59
Cardiac index (min/m^2)	2.3 ± 0.5	2.0 ± 1.0	2.1 ± 0.9	0.31
Systolic blood pressure (mmHg)	107.8 ± 31.6	100.6 ± 18.3	95.6 ± 11.0	0.87
Diastolic blood pressure (mmHg)	71.4 ± 20.6	64.2 ± 19.8	62.8 ± 9.1	0.85
Pulmonary artery diastolic pressure (mmHg)	10.8 ± 2.7	21.9 ± 5.7	33.5 ± 10.3	**<0.001**
Pulmonary artery wedge pressure (mmHg)	11.9 ± 5.3	19.6 ± 5.5	27.9 ± 7.1	**<0.001**
PVR (Wood unit)	3.3 ± 1.6	4.3 ± 2.7	5.6 ± 2.4	**0.007**
Right atrial pressure (mmHg)	8.9 ± 6.6	11.9 ± 3.6	12.9 ± 5.9	0.23
Intraoperative				
Aortic cross-clamping time (min)	40.7 ± 16.6	40.8 ± 12.0	46.7 ± 10.8	0.28
CPB time (min)	127.3 ± 23.5	152 ± 41.3	169 ± 40.4	0.21
Postoperative				
Intensive care unit time (hour)	272.3 ± 142.7	476.5 ± 334.6	369.7 ± 228.8	0.071
Mechanical ventilation time (hour)	53 ± 17.3	133.8 ± 173.7	45.9 ± 29.3	0.71
Left ventricular end-diastolic dimension (mm)	42.3 ± 7.1	45.1 ± 3.1	41.6 ± 4.3	0.26
Left ventricular ejection fraction (%)	60.6 ± 6.4	60.7 ± 4.6	64.2 ± 2.8	**0.019**
Brain natriuretic peptide (ng/L)	10082.6 ± 10413.3	2606.4 ± 2009.4	9138 ± 6781.2	0.12
Cardiac troponin T (μg/L)	0.6 ± 0.5	0.5 ± 0.1	0.9 ± 0.6	0.13
Total cholesterol (mmol/l)	16.8 ± 8.6	22.4 ± 16.9	30.6 ± 19.3	0.68
Albumin (g/L)	38.1 ± 7.2	42.7 ± 6.4	37.2 ± 3.3	0.55
Alanine aminotransferase (IU/L)	24.6 ± 28.7	28.6 ± 18.1	21.6 ± 11.8	0.25
Aspartate aminotransferase (IU/L)	18.4 ± 21.0	17.6 ± 5.8	21 ± 15.2	0.15
Lactate dehydrogenase (U/L)	279.7 ± 97.9	333 ± 68.7	315.4 ± 74.5	**0.032**
Glomerular filtration rate (ml/min)	64.6 ± 36.2	71.9 ± 29.3	73.2 ± 24.9	0.7
Serum creatinine (μmoI/L)	153.7 ± 129.0	99.9 ± 36.5	113 ± 40.5	0.67
Renal replacement therapy (%)	7 (25%)	9 (23.7%)	8 (22.2%)	0.97
ECMO (%)	1 (3.6%)	12 (31.6%)	11 (30.6%)	**0.007**

Data are presented as mean ± standard deviation or n (%). PASP: pulmonary artery systolic pressure; PVR: pulmonary vascular resistance; CPB: cardiopulmonary bypass; ECMO: extracorporeal membrane oxygenation. Bold values mean the P value was less than 0.05, which was considered statistically significant.

hypertrophic cardiomyopathy ($n = 3$), valvular cardiomyopathy ($n = 3$), arrhythmogenic right ventricular cardiomyopathy ($n = 1$), and congenital heart anomaly ($n = 1$). The overall 30-day survival was 91.9%. The 30-day survivals in patients with PASP <35 mmHg, 35–50 mmHg, and ≥50 mmHg were 96.4%, 85.7%, and 89.6%, respectively.

We stratified patients into 3 groups based on their PASPs: <35 mmHg ($n = 28$, 27.5%), 35–50 mmHg ($n = 38$, 37.3%), and >50 mmHg ($n = 36$, 35.3%). Among patients undergoing pulmonary vasodilatory tests, 11 (30.6%) were sufficiently responsive. Baseline characteristics and perioperative data were compared across the 3 groups (Table 1). There was no significant difference in age, gender, graft ischemic time, and preoperative lab tests in patients with different baseline PASPs. As expected, higher PASP was associated with higher pulmonary artery diastolic pressure, pulmonary artery wedge pressure, and PVR (all $P < 0.01$).

3.2. Postoperative ECMO Support. Of the 102 patients, 24 (23.5%) required ECMO support. The support time ranged from 12 hours to 704 hours (mean 167.4 ± 146.4 hours;

Table 2: Characteristics of HTx recipients with and without postoperative ECMO support.

Demographics	ECMO $n = 24$	No ECMO $n = 78$	P value
Age (years)	47.6 ± 15.8	48.7 ± 12.4	0.96
Body mass index (kg/m^2)	22.8 ± 3.2	22.6 ± 3.2	0.8
Female (%)	6 (25%)	17 (21.8%)	0.74
Prior cardiac surgery (%)	4 (16.7%)	11 (14.1%)	0.76
Ischemic time (min)	227.5 ± 120.4	203 ± 105.3	0.97
Preoperative			
Brain natriuretic peptide (ng/L)	6620.2 ± 6017.2	4723.4 ± 4916.3	0.2
Cardiac troponin T (μg/L)	0.1 ± 0.2	0.1 ± 0.4	0.94
Total cholesterol (mmol/l)	30.5 ± 20.8	26.2 ± 20.9	0.29
Albumin (g/L)	46.5 ± 23.5	41.5 ± 7.1	0.79
Alanine aminotransferase (IU/L)	26.2 ± 18.9	41.7 ± 89.3	0.37
Aspartate aminotransferase (IU/L)	27.6 ± 12.0	41.9 ± 48.8	0.34
Lactate dehydrogenase (U/L)	416.1 ± 235.4	275.2 ± 109.7	**0.035**
Glomerular filtration rate (ml/min)	63.7 ± 25.8	71.9 ± 29.1	0.36
Serum creatinine (μmoI/L)	110.5 ± 51.5	123.0 ± 94.6	0.76
Left ventricular end-diastolic dimension (mm)	69.5 ± 11.5	65.2 ± 14.6	0.22
Left ventricular ejection fraction (%)	30.6 ± 9.3	32.0 ± 15.0	0.49
Cardiac output (L/min)	3.9 ± 1.4	3.7 ± 1.3	0.54
Cardiac index (min/m^2)	2.3 ± 0.7	2.4 ± 1.5	0.64
Systolic blood pressure (mmHg)	102.1 ± 17.9	101.8 ± 18.5	0.67
Diastolic blood pressure (mmHg)	63.4 ± 12.1	63.6 ± 13.8	0.58
PASP (mmHg)	52.9 ± 19.0	43.6 ± 14.8	**0.024**
Pulmonary artery diastolic pressure (mmHg)	24.7 ± 11.5	20.3 ± 11.1	0.072
Pulmonary artery wedge pressure (mmHg)	23.6 ± 8.3	20.0 ± 8.5	0.13
PVR (Wood unit)	3.9 ± 2.6	4.4 ± 2.5	0.42
Right atrial pressure (mmHg)	13.8 ± 7.9	11.8 ± 5.9	0.36
Intraoperative			
Aortic cross-clamping time (min)	54.6 ± 20.4	48.3 ± 17.0	0.19
CPB time (min)	247.7 ± 73.1	168.4 ± 67.9	**<0.001**
Postoperative			
Intensive care unit time (hour)	501.4 ± 307.1	384.6 ± 313.0	**0.036**
Mechanical ventilation time (hour)	197.0 ± 102.1	62.1 ± 59.0	**<0.001**
Left ventricular end-diastolic dimension (mm)	40.9 ± 4.8	43.2 ± 4.6	**0.021**
Left ventricular ejection fraction (%)	58.7 ± 13.0	62.2 ± 5.5	0.74
Brain natriuretic peptide (ng/L)	13049.9 ± 12787.7	7032.2 ± 9752.5	**0.016**
Cardiac troponin T (μg/L)	1.4 ± 2.1	0.7 ± 0.8	**0.032**
Total cholesterol (mmol/l)	76.8 ± 82.6	30.1 ± 45.2	0.2
Albumin (g/L)	40.0 ± 4.7	38.8 ± 5.8	0.2
Alanine aminotransferase (IU/L)	36.3 ± 52.6	27.6 ± 25.3	0.27
Aspartate aminotransferase (IU/L)	36.5 ± 34.3	22.4 ± 19.1	**0.019**
Lactate dehydrogenase (U/L)	549.2 ± 484.9	317.5 ± 108.7	**<0.001**
Glomerular filtration rate (ml/min)	56.6 ± 31.0	69.3 ± 31.2	0.078
Serum creatinine (μmoI/L)	154.7 ± 90.2	135.8 ± 99.9	0.055
Renal replacement therapy (%)	10 (41.7%)	14 (17.9%)	**0.017**

Data are presented as mean ± standard deviation or n (%). PASP: pulmonary artery systolic pressure; PVR: pulmonary vascular resistance; CPB: cardiopulmonary bypass; ECMO: extracorporeal membrane oxygenation. Bold values mean the P value was less than 0.05, which was considered statistically significant.

median 136 hours). In 20 (83.3%) patients, ECMO was initiated intraoperatively due to the difficulty in weaning from CPB. Hemodynamic instability was corrected by ECMO in 2 (8.3%) patients within 24 hours in the intensive care unit, and in 2 (8.3%) patients in 24–72 hours following HTx. Right ventricular failure was the major form of graft dysfunction ($n = 12$, 50.0%), followed by left ventricular failure ($n = 5$, 20.8%) and biventricular failure ($n = 7$, 29.2%). Patients with ECMO support had higher baseline PASP (52.9 ± 19.0 mmHg vs. 43.6 ± 14.8 mmHg, $P = 0.024$), longer CPB time (247.7 ± 73.1 minutes vs. 168.4 ± 67.9 minutes, $P < 0.001$), longer intensive care unit stay time (501.4 ± 307.1 hours vs. 384.6 ± 313.0 hours, $P = 0.036$), and longer mechanical ventilation time (197.0 ± 102.1 hours vs. 62.1 ± 59.0 hours, $P < 0.001$; Table 2). Continuous renal replacement therapy was more commonly used in patients supported with ECMO (41.7% vs. 17.9%, $P = 0.017$). Within 24 hours after HTx, patients who received ECMO support had higher levels of B-type natriuretic peptide, cardiac troponin T, and liver enzymes. The 30-day actuarial survivals in patients with and without ECMO support were 72.5% and 95.4%, respectively. Kaplan–Meier analysis and log-rank test showed a trend toward higher mortality in patients receiving ECMO support ($P = 0.053$; Figure 1).

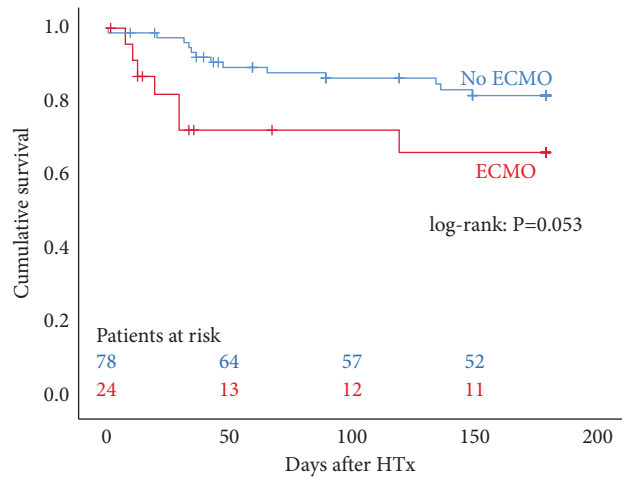

Figure 1: Kaplan–Meier curves of survival between HTx recipients with and without postoperative ECMO support.

3.3. Relationship between PASP and ECMO Support. Through the comparison between the groups with and without ECMO support, we had found that patients with ECMO support had a higher baseline PASP. ECMO support was significantly more common in patients with PASP 35–50 mmHg ($n = 12$, 31.6%) and PASP >50 mmHg ($n = 11$, 30.6%) than in those with PASP <35 mmHg ($n = 1$, 3.6%; $P = 0.007$). Among 11 patients with PASP >50 mmHg who underwent ECMO support, 4 (36.4%) were responsive to vasodilation. Using univariate logistic analysis, several predictors of ECMO support were selected, including pretransplant PASP group (odds ratio [OR], 2.159; 95% confidence interval [CI], 1.132–4.118; $P = 0.02$), preoperative use of sacubitril/valsartan (OR, 0.286; 95% CI, 0.078–1.046; $P = 0.059$), and total CPB time (OR, 1.014; 95% CI, 1.007–1.021; $P < 0.001$; Table 3). Multivariate analysis demonstrated pretransplant PASP group was independently associated postoperative ECMO support (OR, 2.344; 95% CI, 1.099–5.000; $P = 0.028$; Table 3). After adjusting preoperative age, gender, comorbidities and medications, mortality was not significantly different between patients with PASP >50 mmHg and PASP <35 mmHg (log-rank, 0.47; adjusted $P = 0.64$) or between those with PASP 35–50 mmHg and PASP <35 mmHg (log-rank, 1.15; adjusted $P = 0.25$).

4. Discussion

In the current study, we observed a positive correlation between pretransplant PASP 35–50 mmHg and increase in posttransplant ECMO use, the latter of which was likely to be associated with early mortality.

Pulmonary hypertension is a well-reported risk factor for graft dysfunction and mortality after HTx. The current guidelines for HTx recommend vasodilator challenge and medical optimization in patients with PASP ≥50 mmHg [6], while the benefit of lowering pulmonary artery pressure in HTx candidates with mildly elevated PASP was less studied. Over 20 years ago, Delgado et al. reported that mild pulmonary hypertension was a risk factor for posttransplant mortality [10]. However, in their study, the patients with mild pulmonary hypertension were in the same group with those with severe pulmonary hypertension, and subgroup analysis was not performed. Using the United Network for Organ Sharing registry database, Vakil et al. reported that mild pulmonary hypertension, defined as pulmonary vascular resistance 2.5–3.4 Wood units, transpulmonary gradient 13–16 mmHg and mean pulmonary artery pressure 25–34 mmHg, was related to a modest increase in posttransplant mortality [11]. Consistently, in this study, our findings demonstrated that pretransplant PASP 35–50 mmHg was clinically meaningful and could lead to severe graft dysfunction (mostly right ventricular dysfunction) requiring ECMO support.

In this study, the rate of ECMO support was 23.5%, which was within the wide range from 2.1% to 31.6% as reported in previous studies [12–16]. Our institution adopts an active, prompt protocol and initiates ECMO support for almost every recipient with significant graft dysfunction, which may contribute to the high ECMO rate. Another reason is that ventricle assist devices are not clinically available in our country, and the experience of percutaneous mechanical circulatory support is lacking, making ECMO the only available option for graft dysfunction after heart transplantation.

The use of ECMO for the management of primary graft dysfunction is associated with significant posttransplant morbidity and mortality. The 1-year survival in HTx patients undergoing ECMO support for severe graft dysfunction was 57.9% in Stanford University School of Medicine [17]. The 30-day survivals for this patient cohort were 43% in Cleveland Clinic [18] and <40% in Heinrich-Heine-University Medical School [12]. The in-hospital mortality was 39% in Mayo Clinic [19]. In this study, the 30-day survival of patients receiving ECMO support was 72.5%. In over 90% cases, ECMO were initiated for severe graft dysfunction within 24 hours after HTx. With advances in the management of the related complications, ECMO support was nonetheless associated with a higher early mortality despite a borderline P value (Figure 1), mostly due to multiorgan dysfunction and persistent circulatory failure. In this regard, risk factors such as pretransplant PASP should be rigorously optimized to reduce ECMO use.

Our data demonstrated a nonlinear, S-shaped relationship between PASP and ECMO use, where a steep increase in ECMO use was identified between 35 and 50 mmHg of PASP. The proposal of the cutoff value of PASP (35 mmHg) and delineation of the PASP–ECMO correlation are the new information of this study. Using univariate logistic analysis, the result suggested that PVR was not a predictor for postoperative ECMO support (OR, 0.92; 95% CI, 0.727–1.165; $P = 0.489$). The correlation with ECMO use was more evident with PASP than PVR. However, PASP is believed to be a fluctuating parameter that is sensitive to volume status, pulmonary resistance, and cardiac output [8, 20]. In this study cohort, the PASP was measured in patients optimized with oral medical therapies, suggestive of a relatively stable level. Interestingly, the correlation with

Table 3: Risk factors for ECMO support after transplant.

	Univariate model		*Multivariate model*	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
PASP (per degree)	2.159 (1.132–4.118)	0.02	2.344 (1.099–5)	0.028
CPB (min)	1.014 (1.007–1.021)	<0.001	1.014 (1.007–1.021)	<0.001
Preoperative use of sacubitril/valsartan	0.286 (0.078–1.046)	0.059		

CI: confidence interval; OR: odds ratio; PASP: pulmonary artery systolic pressure; CPB: cardiopulmonary bypass.

ECMO use was more evident with PASP than with other right heart catheterization parameters such as PVR. Similarly, two HTx groups reported that PASP had higher prognostic value for posttransplant survival than PVR [21, 22]. In this study, pulmonary artery wedge pressure and PVR were significantly different across the 3 groups and were in inverse correlations with left ventricular end-diastolic dimension and ejection fraction, which indicated the secondary nature of elevated PASP. There was another possibility that insufficient diuresis existed in some patients with elevated PASP at the time of right heart catheterization. More data are warranted to determine whether the assessment of PASP reversibility could give better prognostic information than PVR reversibility.

This study was based on the real-world practice at our institution. Although primary pulmonary hypertension and cyanotic congenital heart disease constitute definite contraindications for HTx, it is not easy to turn down a deteriorating patient with secondary pulmonary hypertension in our country where ventricular assist devices are not adequately available [23]. According to one United Network for Organ Sharing registry analysis of 26649 patients receiving HTx, 8980 (33.7%) had pulmonary hypertension that was determined by the latest right heart catheterization prior to transplant, and 4323 (16.2%) of them had moderate-to-severe pulmonary hypertension [11], indicating that elevation of pulmonary artery pressure is a common yet intractable issue in HTx recipients.

The present study displays several limitations. First, this study is a retrospective, single-center investigation that could be potentially biased by its nature. The sample size is relatively small that could undermine the statistical power of multivariate analysis. In addition, donors' body surface area and weight were not shown in the earlier versions of the organ sharing system, which precluded comparison of the donor and recipient body sizes. Moreover, the decision to initiate ECMO or not was dependent on the graft function, which could be contributed by nongraft factors such as CPB support time, volume status, and degree of acidosis. In addition, the right heart catheterization data utilized in this study were the latest one prior to transplant. Given that the median waiting time was 3 months at our institution, the majority of the HTx candidates received only one right heart catheterization. Besides, there were significant data missing in the donors' weight and body surface area that precluded further analysis. Lastly, the lack of right heart catheterization data before induction of anesthesia failed to provide longitudinal evidence of responsiveness to inotrope or vasodilator therapies. We believe that many patients with pulmonary hypertension at the time of listing could have reduced PASP during HTx due to intensified medical treatment. Unfortunately, such hypothesis cannot be fully validated in the present study.

5. Conclusion

Mildly elevated PASP represents an independent predictor for ECMO support following HTx. Prompt medical management should be considered in patients with pretransplant PASP ≥35 mmHg.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Additional Points

Reporting Checklist. The authors have completed the ARRIVE reporting checklist.

Ethical Approval

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Medical Ethics Committee (No. B2021-668R).

Consent

Individual consent for this retrospective analysis was waived.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Li Yuan, Wenruit Ma, and Jie Cui were involved in data collection, design, analysis manuscript preparation. Junjiang Liu, Zhaohua Yang, Shouguo Yang, Hongqiang Zhang, and Fanshun Wang were involved in design and editing. Chunsheng Wang and Xiaoning Sun were involved in concept, data collection, analysis, manuscript preparation, and editing. Li Yuan, Wenrui Ma, and Jie Cui contributed equally to this study.

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