How does severe functional mitral regurgitation redefined by European guidelines affect pulmonary vascular resistance and hemodynamics in heart transplant candidates?

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Abstract

Objective: Increased pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) are important prognostic factors in patients with heart transplantation (HT). It is well known that severe mitral regurgitation increases pulmonary pressures. However, the European Society of Cardiology and the 6th World Symposium of pulmonary hypertension (PH) task force redefined severe functional mitral regurgitation (FMR) and PH, respectively. We aimed to investigate the effect of severe FMR on PAP and PVR based on these major redefinitions in patients with HT.

Methods: A total of 212 patients with HT were divided into 2 groups: those with severe FMR (n=70) and without severe FMR (n=142). Severe FMR was defined as effective orifice regurgitation area ≥20 mm^2 and regurgitation volume ≥30 mL where the mitral valve was morphologically normal. A mean PAP of >20 mm Hg was accepted as PH. Patients with left ventricular ejection fraction ≤25% were included in the study.

Results: The systolic PAP, mean PAP, and PVR were higher in patients with severe FMR than in those without severe FMR [58.5 (48.0–70.2) versus 45.0 (36.0–64.0), p<0.001; 38.0 (30.2–46.6) versus 31.0 (23.0–39.5), p=0.004; 4.0 (2.3–6.8) versus 2.6 (1.2–4.3), p=0.001, respectively]. Univariate analysis revealed that the severe FMR is a risk factor for PVR ≥3 and 5 WU [odds ratio (OR): 2.0, 95% confidence interval (CI): 1.1–3.6, p=0.009; and OR: 3.2, 95% CI: 1.5–6.7, p=0.002]. The multivariate regression analysis results revealed that presence of severe FMR is an independent risk factor for PVR ≥3 WU and presence of combined pre-post-capillary PH (OR: 2.23, 95% CI: 1.30–3.82, p=0.003 and OR: 2.30, 95% CI: 1.25–4.26, p=0.008).

Conclusion: Even in the updated definition of FMR with a lower threshold, severe FMR is associated with higher PVR, systolic PAP, and mean PAP and appears to have an unfavorable effect on pulmonary hemodynamics in patients with HT.

Keywords: heart transplantation, pulmonary hypertension, pulmonary vascular resistance, severe heart failure, severe functional mitral regurgitation

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Introduction

End-stage heart failure is a lethal syndrome, with heart transplantation (HT) being the gold standard for treatment. Pulmonary hypertension (PH) and increased pulmonary vascular resistance (PVR) are important risk factors for right heart failure and mortality after HT. The guidelines of the International Society for Heart and Lung Transplantation (ISHLT) recommend serial right heart catheterizations (RHCs) at 3-month intervals in patients with HT, with pulmonary vasodilator testing for patients having PVR ≥3 WU (1). Fixed PH, defined as PVR ≥5 WU despite aggressive treatment with one or more inotropes or pulmonary vasodilators,

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HIGHLIGHTS

- The patients with severe FMR have a higher PVR value and pulmonary pressures.
- The patients with severe FMR have increased rate of PVR ≥3 and PVR ≥5 WU.
- Grade 3 LV diastolic dysfunction is the first and severe FMR is the second most important risk factor for the presence of PVR ≥3 WU.
- Grade 3 LV diastolic dysfunction is the first and severe FMR is the second most important risk factor for the presence of Cpc-PH.

represents a relative contraindication to HT (1-4). Association of PVR with mortality assumes a nonlinear form, with mortality increasing steeply for PVR ≥3 WU (5).

In left heart failure, PH is a common condition and results from pulmonary vasoconstriction and vascular remodeling due to increased left ventricular (LV) filling pressure, which is affected by severity of heart failure, presence of diastolic dysfunction, and valvular regurgitation (6-9). Therefore, any condition that affects LV filling pressures can affect pulmonary pressures or PVR.

Functional mitral regurgitation (FMR) is a frequent complication of severe LV systolic dysfunction and is caused by LV remodeling without organic mitral valve disease (10-13). Hemodynamically severe FMR aggravates LV filling pressures and symptoms and eventually risks survival (11, 14, 15). Previous studies have shown that significant FMR is associated with increased LV end-diastolic, left atrial, pulmonary artery wedge pressure (PAWP), pulmonary artery pressures (PAPs), and PVR measured by RHC (16-18). However, these previous studies mostly involved primary valve pathologies (with relatively low number of patients with FMR), and cutoff values of severe mitral regurgitation (both primary and functional) were considered as effective regurgitation orifice area (EROA) ≥40 mm^2 and regurgitation volume (RV) ≥60 mL. In 2012, the European Society of Cardiology guidelines for management of valvular heart diseases changed the definition of severe FMR and updated the cutoff values as EROA ≥20 mm^2 and RV ≥30 mL (19).

The definition of PH was updated by the 6th World Symposium of pulmonary hypertension (WSPH) task force to mean PAP >20 mm Hg instead of ≥25 mm Hg (20). After this definition, the frequency of the overall diagnosis of PH in patients with end-stage heart failure seems to have increased. Since the updated definition of severe FMR, few studies have been performed to assess how severe FMR affects pulmonary hemodynamic parameters, measured using RHC. In addition, there has been no study after redefinition of PH by WSPH. This study aimed to investigate how severe FMR affects pulmonary hemodynamics, PVR, and the frequency of PH, even at low threshold values.

Methods

Patient population

A total of 212 patients with end-stage heart failure referred for HT were consecutively enrolled in the study. On the basis of echocardiographic findings, the study population was divided into 2 groups: those with severe FMR and those without severe FMR. Patients with moderate, mild, and no mitral regurgitations were included in the group without severe FMR. The inclusion criteria were age ≥18 years, left ventricular ejection fraction (LVEF) ≤25%, New York Heart Association (NYHA) functional class III–IV, interagency registry for mechanically assisted circulatory support (INTERMACS) level IV–VI, and measurable mitral valve function by color and speckle Doppler echocardiography. Exclusion criteria were primary mitral valve pathology; prior valvular surgery; severe aortic regurgitation; age ≥70 years; inotropic dependency; need for an intra-aortic balloon pump; multi-organ deficiency; infiltrative, constrictive, or hypertrophic cardiomyopathy; congenital heart disease; history of moderate or severe chronic obstructive pulmonary disease or primary lung disease; serum creatinine level ≥2.5 mg/dL; and comorbidities causing contraindication to HT determined by ISHLT. The patients who refused to enter the study were also excluded. The study was approved by the Local Ethics Board.

Echocardiographic measurements

The LVEF was determined by biplane Simpson's method. The size of the left atrium (LA), left and right ventricle, LV diastolic function parameters such as ratio of early transmitral flow velocity (E) to early diastolic mitral annular velocity (e') and deceleration time (DT) of mitral E-wave, systolic PAPs, PVR, tricuspid annular plane systolic excursion (TAPSE), systolic tricuspid velocity (ST), and plethora were measured. EROA and RV were calculated using the proximal isovelocity surface area (PISA) method to differentiate severe FMR from moderate FMR. Severe FMR was defined as EROA ≥20 mm^2 and RV ≥30 mL when the mitral valve was morphologically normal. Trace and mild mitral regurgitation were visually classified as without FMR because PISA could not be measured in most of these patients.

Invasive hemodynamic measurements

The acute decompensated patients were medically treated before catheterization. RHC was performed with a Swan-Ganz catheter, and the LV and aortic pressures were assessed with a pigtail catheter with hemodynamic and fluoroscopic guidance. The pulmonary artery systolic, mean, and diastolic pressures (PAPs, PAPm, and PAPd, respectively); PAWP; mean right atrial pressure (RAPm); transpulmonary gradient (TPG); PVR; right ventricle stroke work index [RVSWI = (PAPm-RAPm) × SVI × 0.0136]; systolic blood pressure (SBP); diastolic blood pressure (DBP), LV end-diastolic pressure (LVEDP), trans-systemic gradient (TSG); systemic vascular resistance (SVR); cardiac output (CO) by direct Fick method; cardiac index; stroke volume (SV); stroke volume index (SVI); and LV stroke work index [LVSWI = (mean aortic pressure-PAWP) × SVI × 0.0136] were measured.

Hemodynamic definition

The definition and classification was performed according to the 6th WSPH task force recommendation (20). PH was defined as PAPm ≥20 mm Hg assessed by RHC. The isolated post-capillary pulmonary hypertension (Ipc-PH) was defined as PAPm ≥20 mm Hg, PAWP ≥15 mm Hg, and PVR <3 WU. The combined pre- and post-capillary PH (Cpc-PH) was defined as PAPm ≥20 mm Hg, PAWP≥15 mm Hg, and PVR ≥3 WU. The pre-capillary PH was defined as PAPm ≥20 mm Hg, PCWP <15 mm Hg, and PVR ≥3 WU (20).

Statistical analysis

Values for normally distributed continuous variables were expressed as the means, while values for not normally distributed variables were expressed as medians (interquartile range). Group comparisons for continuous variables were analysed by using independent t-test if data distribution was normal. Mann-Whitney test was used for group comparisons of continuous variables if data distribution was not normal. Comparisons of categorical variables were evaluated by the chi-square test.

Primary outcome: Presence of pulmonary vascular resistance ≥3 WU in patients with heart transplant.

Statistical modeling: The putative predictors were included in the statistical model, and their association with PVR ≥3 WU/presence of Cpc-PH had been demonstrated according to previous studies. Variables with very low and very high frequencies were not included in the model. Because of our outcome of variable dichotomus, we preferred to use binary logistic regression. The primary outcome in the first model (PVR ≥3 WU) and second model (presence of Cpc-PH) model included 6 predictor variables, including heart failure type (non-ischemic and ischemic), heart failure duration, severe FMR, LVESD, LVEF, and LV diastolic dysfunction. Effect of individual predictors on PVR ≥3 WU/presence of Cpc-PH (outcome variable) was reported by using odds ratio (OR) and 95% confidence interval (CI).

The relative importance of each predictor in the models was estimated with a partial X2 value for each predictor, divided by the model's total X2, which estimates the independent contribution of the predictor to the variance of the outcome. The calibration was assessed by plotting the observed outcome on the Y-axis and the predicted outcome on the X-axis. The primary purpose of the partial effect plot was to show the relationship between 2 plotted variables [PVR ≥3 WU/presence of Cpc-PH (outcome) and an explanatory variable] adjusting for interference from other explanatory variables in the model.

Differences were considered statistically significant when the two-sided p value was <0.05. All statistical analyses were performed using R-studio version 4.02 (R statistical software, Institute for statistics and mathematics, Vienna, Austria).

Results

Demographic and clinical characteristics

The baseline demographic and clinical measures of the patients are summarized in Table 1. Among the 212 study patients, 70 (33.0%) were included in the group with severe FMR and 142 (66.9%) were included in the group without severe FMR. Patients in both the groups were similar in terms of age and sex. Body mass index, hypertension, diabetes, hyperlipidemia, prior coronary arterial bypass grafting, smoking, atrial fibrillation, obesity, and heart failure duration were also similar between the 2 groups. Higher incidences of cerebrovascular disease and chronic obstructive pulmonary disease were documented in the group without severe FMR (p=0.035 and p=0.022). Although the rate of non-ischemic cardiomyopathy was more common than that of ischemic cardiomyopathy in both the groups, the distribution of ischemic and non-ischemic etiology did not differ between the groups. NYHA functional classes and INTERMACS levels of the 2 groups were also similar (3.2±0.45 versus 3.2±0.44 p=0.740, 4.8±1.6 versus 4.7±1.4 p=0.681, respectively). The serum hemoglobin, creatinine, glomerular filtration rate, and transaminases levels of the groups were not significantly different. However, the serum sodium and albumin levels were lower, whereas bilirubin level was higher in patients with severe FMR (p=0.012, p<0.001, and p=0.043, respectively). The heart failure medications of the patients were similar between the 2 groups (Table 1).

Echocardiographic characteristics

The echocardiographic characteristics of the patients are summarized in Table 2. The mean values of LVEF, E/e' ratio, TAPSE, ST and rate of severe tricuspid regurgitation, right ventricular dilatation, LV diastolic dysfunction grade 3, and plethora were similar among the 2 groups. LA dimension, LA dimension index, LV end-diastolic dimension, and LV end-systolic dimension were found to be higher in patients with severe FMR compared with those without severe FMR (p=0.001, p<0.001, p=0.009, and p=0.009, respectively). The patients with severe FMR had higher PAPs and PVR values than patients without severe FMR [55.0 (50.0–60.0) versus 45.0 (35.0–60.0), p<0.001 and 4.7 (3.5–5.2) versus 3.3 (2.2 versus 4.8), p<0.001, respectively]. The patients with ICMP had lower DT compared with those with NICMP (127.1±4.5 versus 114.9±26.7, p=0.041).

Invasive hemodynamic characteristics

The invasive hemodynamic measures are summarized in Table 3. Severe FMR was related to increased PAPs, PAPm, PAPd, PAWP, RAPm, and TPG (p<0.001, p=0.004, p<0.001, p<0.001, p=0.004, and p=0.004, respectively) but was not related to RVSWI (p=0.179). The patients with severe FMR had significantly higher values of PVR compared with those without severe FMR [4.0 (2.3–6.8) versus 2.6 (1.2–4.3), respectively; p=0.001]. Among the left heart catheterization findings, SBP, TSG, CO, CI, SV, SVI, and LVSWI were significantly lower in patients with severe FMR compared with those without severe FMR (Table 3).

The rates of PVR ≥3 and PVR ≥5 WU were higher in the group with severe FMR than in the group without severe FMR (63.2% versus 45.0%, p=0.009 and 28.9% versus 12.0%, p=0.002, respectively) (Fig. 1). Univariate logistic regression analysis revealed that severe FMR is a risk factor for PVR ≥3 and 5 WU (OR: 2.0, 95% CI: 1.1–3.6, p=0.009; and OR: 3.2, 95% CI: 1.5–6.7, p=0.002).

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Table 1. Demographic and clinical characteristics of the patients with and without FMR

Baseline characteristics	Severe FMR (n=70)	Without severe FMR (n=142)	*P*-value
Age (years, median)	49.0 (36.7-56.0)	48.0 (40.0-54.0)	0.721
Males (n, %)	63 (90.0)	126 (88.7)	0.808
BMI (kg/m^2)	24.7 (21.5-28.5)	25.8 (23.1-28.9)	0.194
Comorbidities (n, %)			
Hypertension	10 (14.2)	40 (28.5)	0.022
Diabetes	12 (17.1)	30 (21.1)	0.862
Hyperlipidemia	16 (22.8)	37 (26.4)	0.672
CAD	32 (45.7)	67 (47.8)	0.872
CVD	0 (0)	9 (6.0)	0.035
COPD	1 (1.4)	6 (4.2)	0.022
Smoking	26 (34.2)	64 (39.0)	0.292
Atrial fibrillation	7 (14.2)	20 (14.2)	0.408
Obesity	10 (14.2)	27 (19.2)	0.358
HF duration	3.0 (1.8-7.2)	3.0 (1.0-6.0)	0.225
Etiology of heart failure (n, %)			
Ischemic	32 (45.7)	65 (46.4)	0.677
Nonischemic	38 (54.2)	75 (53.5)	
NYHA (mean)	3.2±0.45	3.2±0.44	0.740
INTERMACS (mean)	4.8±1.6	4.7±1.4	0.681
Haemoglobin (g/dL, median)	12.2 (10.8-14.0)	13.1 (11.4-14.4)	0.075
Creatinin (mg/dl, median)	0.9 (0.77-1.2)	0.9 (0.77-1.1)	0.413
GFR (ml/min/1.73 m^2, median)	100.9 (63.0-128.0)	102.1 (78.0-137.0)	0.221
Sodium (mEq/L, median)	134.0 (130.0-137.0)	136.0 (134.0-138.0)	0.012
Albumin (mg/dL, median)	3.8 (3.0-4.1)	4.2 (3.7-4.5)	<0.001
Bilirubin (mg/dL, median)	1.2 (0.87-2.2)	1.0 (0.54-2.0)	0.043
Heart failure medications (n, %)			
Beta blockers	63 (90)	123 (87.8)	0.734
ACEI or ARB	59 (84.2)	113 (79.5)	0.832
Spirinolactone	45 (64.2)	95 (66.9)	0.444
Diuretics	66 (94.2)	137 (96.4)	0.289
Ivabradin	15 (21.4)	30 (21.1)	0.786
Digoxin	14 (20.0)	31 (21.8)	0.654
Secubitril/valsartan	10 (14.2)	22 (15.4)	0.453

Values are presented as mean±SD, % of cohort, or median (25th-75th percentile). Severe FMR was defined as EROA ≥0.2 cm^2 and RV ≥30 ml, and mitral valve was morphologically normal.
ACEI - angiotensin-converting enzyme inhibitor; ARB - angiotensin receptor blocker; BMI - body mass index; CAD - coronary artery disease; COPD - chronic obstructive pulmonary disease; CVD - cerebrovascular disease; EROA – effective regurgitation orifice area; FMR - functional mitral regurgitation; GFR - glomerular filtration rate; HF - heart failure; INTERMACS - Interagency Registry for Mechanically Assisted Circulatory Support; NYHA - New York Heart Association; RV – right ventricle

Table 2. Echocardiographic findings of the patients with and without severe FMR

Variable	Severe FMR (n=70)	Without severe FMR (n=142)	*P*-value
Echocardiography			
LAD (cm)	4.9 (4.5-5.3)	4.7 (4.3-5.0)	0.001
LADI (cm/m^2)	2.6 (2.4-3.0)	2.5 (2.3-2.7)	<0.001
LVEDD (cm)	7.1 ±0.86	6.8±0.92	0.009
LVESD (cm)	6.2±0.92	5.8±0.99	0.009
LVEF (%)	21.0±4.9	20.3±4.8	0.387
MV E/E'	17.1±5.8	15.8±7.3	0.193
MV DT (msn)	127.1±4.5	114.9±26.7	0.041
Severe tricuspid insufficiency (n, %)	23 (32.8)	31 (21.8)	0.068
LVDD grade 3 (n, %)	54 (77.1)	103 (72.5)	0.291
PAPs (mm Hg)	55.0 (50.0-60.0)	45.0 (35.0-60.0)	<0.001
PVR (Wood units)	4.7 (3.5-5.2)	3.3 (2.2-4.8)	<0.001
TAPSE (mm)	1.4±0.36	1.5±0.5	0.355
ST (cm/sec)	9.4±2.8	9.3±2.3	0.791
RV dilatation (n, %)	34 (48.5)	37 (26.0)	0.051
Plethora (n, %)	18 (25.7)	36 (25.3)	0.878

Values are presented as mean±SD, % of cohort, or median (25th-75th percentile). Severe FMR was defined as EROA ≥20 mm^2 and RV ≥30 ml, and mitral valve was morphologically normal.
FMR - functional mitral regurgitation; LAD - left atrial dimension; LADI - left atrial dimension index; LVDD - left ventricular diastolic dysfunction; LVEDD - left ventricular end-diastolic dimension; EROA – effective regurgitation orifice area; LVEF - left ventricular ejection fraction; LVESD - left ventricular end-systolic dimension; MV - mitral valve; MV DT - mitral valve deceleration time; PAPs - systolic pulmonary arterial pressure; PVR - pulmonary vascular resistance; RV - right ventricle; ST - systolic tricuspid velocity; TAPSE - tricuspid annular plane systolic excursion

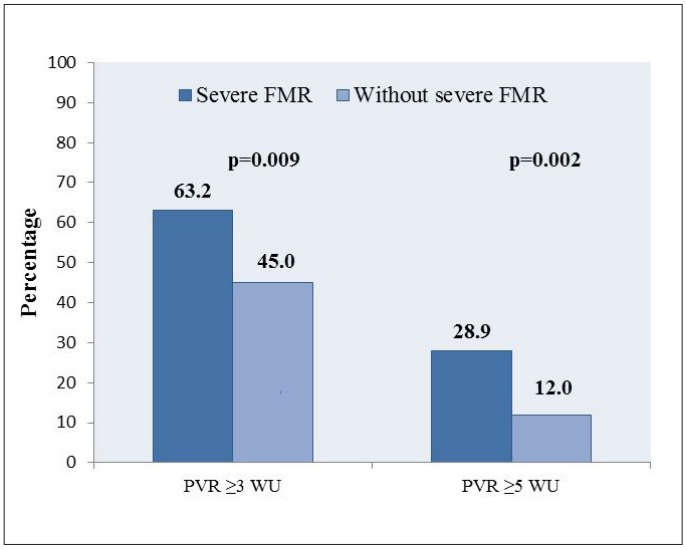

Figure 1. The percentages of the patients with PVR ≥3 and ≥5 WU in patients with and without severe FMR. It was clearly seen that more patients with PVR ≥3 WU and PVR ≥5 WU were found in the group with severe FMR
FMR - functional mitral regurgitation; PVR - pulmonary vascular resistance; WU - Wood unit

Table 3. Invasive hemodynamic features of the patients with and without severe FMR

Invasive hemodynamics	Severe FMR (n=70)	Without severe FMR (n=142)	*P*-value
PAPs (mm Hg, median)	58.5 (48.0-70.2)	45.0 (36.0-64.0)	<0.001
PAPm (mm Hg, median)	38.0 (30.2-46.6)	31.0 (23.0-39.5)	0.004
PAPd (mm Hg, median)	25.5 (20.0-33.0)	21.0 (14.0-27.0)	<0.001
PAWP (mm Hg, median)	25.0 (20.0-30.0)	21.0 (16.5-27.0)	<0.001
RAP (mm Hg, median)	12.0 (8.0-17.7)	9.0 (5.0-15.0)	0.004
TPG (mm Hg, median)	11.0 (7.0-18.0)	8.0 (5.0-15.0)	0.004
PVR (WU, median)	4.0 (2.3-6.8)	2.6 (1.2-4.3)	0.001
RVSWI (g/m^2/beat)	6.21 (4.6-8.4)	5.7 (4.0-7.7)	0.179
SAP (mm Hg, median)	101.0 (90.5-114.0)	110.0 (95.5-121.5)	0.005
DAP (mm Hg, mean)	64.9±11.1	66.7±15.1	0.342
LVEDP (mm Hg, median)	28.5 (23.0-33.0)	23.0 (19.0-29.25)	<0.001
TSG (mm Hg, median)	66.5 (58.0-74.0)	70.0 (60.0-81.0)	0.021
SVR (WU, men)	21.7 ±8.1	21.6±8.0	0.920
CO (l/min, median)	3.0 (2.5-3.5)	3.5 (2.8-4.8)	0.004
CI (l/min/m^2, median)	1.6 (1.4-1.8)	1.8 (1.5-2.1)	0.009
SV (ml/beat, mean)	37.0 ±10.3	43.0±15.0	0.001
SVI (ml/m^2/beat, mean)	19.9±5.3	23.0±8.1	0.004
LVSWI (g/m^2/beat, median)	13.4 (10.8-18.4)	17.2 (12.7-24.7)	<0.001

Values are presented as mean±SD, % of cohort, or median (25th-75th percentile). Severe FMR was defined as EROA ≥20 mm^2 and RV ≥30 ml, and mitral valve was morphologically normal.
CI - cardiac index; CO - cardiac output; DAP - diastolic aortic pressure; FMR - functional mitral regurgitation; LVEDP - left ventricle end-diastolic pressure; LVSWI - left ventricular stroke work index; EROA – effective regurgitation orifice area; PAPd - diastolic pulmonary artery pressure; PAPm - mean pulmonary artery pressure; PAPs - systolic pulmonary artery pressure; PAWP - pulmonary artery wedge pressure; PVR - pulmonary vascular resistance; RAP - right atrial pressure; RVSWI - right ventricular stroke work index; SAP - systolic aortic pressure; SV - stroke volume; SVI - stroke volume index; SVR - systemic vascular resistance; TPG - transpulmonary gradient; TSG - trans-systemic gradient; WU - wood units

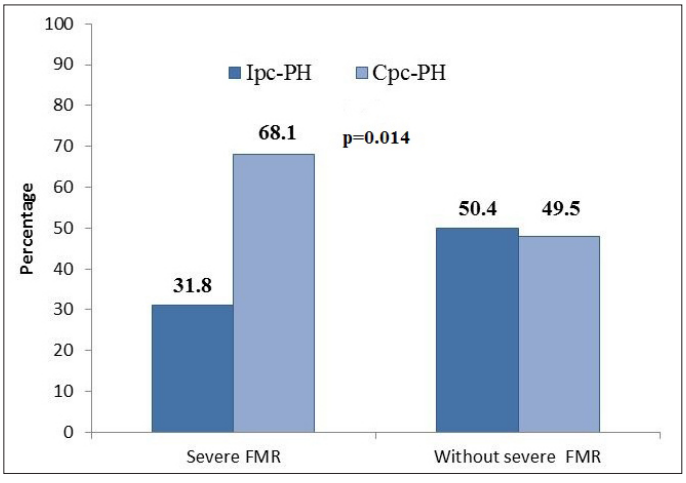

Figure 2. In patients with PH, the rate of Cpc-PH was higher than that of Ipc-PH in patients with severe FMR. However, the rate of Cpc-PH was similar to that of Ipc-PH in patients without severe FMR

Cpc-PH - combined pre-post capillary pulmonary hypertension; FMR - functional mitral regurgitation; Ipc-PH - isolated postcapillary pulmonary hypertension; PH - pulmonary hypertension

The univariate and multivariate logistic regression analyses were performed using possible confounding factors for PVR ≥3 WU in the dataset, including HF type, HF duration, severe FMR, LV end-systolic dimension, LVEF, and LV diastolic dysfunction grade 3 (Table 4). The results of univariate logistic regression revealed that non-ischemic type cardiomyopathy was a negative risk factor for PVR ≥3 WU compared with ischemic type cardiomyopathy (OR: 0.52, 95% CI: 0.33–0.82, p=0.004). Severe FMR, increased LVESD, and LV diastolic dysfunction grade 3 were risk factors for PVR ≥3 WU (OR: 2.27, 95% CI: 1.40–3.69, p<0.001, OR: 1.37, 95% CI: 1.07–1.75, p=0.001, and OR: 2.64, 95% CI: 1.51–4.61, p<0.001; respectively). The results of multivariate logistic regression analysis revealed that the presence of LV diastolic dysfunction grade 3 and severe FMR were risk factors for PVR ≥3 WU, whereas non-ischemic cardiomyopathy was a negative risk factor for PVR ≥3 WU independent from other confounding factors (OR: 2.45, 95% CI: 1.38–4.35, p=0.002; OR: 2.23, 95% CI: 1.30–3.82, p=0.003; and OR: 0.56, 95% CI: 0.34–0.92, p=0.023; respectively) (Table 4).

Among the 212 patients, 187 (88.2%) had PH, 90 (42.9%) had Cpc-PH, and 97 (45.3%) had Ipc-PH. Although more PH was observed in patients with severe FMR than in those without severe FMR (94.2% versus 85.2%), it did not reach statistical significance (p=0.069). The distribution of Ipc-PH and Cpc-PH in patients with PH was similar in patients without severe FMR (50.4% versus 49.5%), but higher incidences of Cpc-PH were found in patients with severe FMR than in those without severe FMR (68.1% versus 31.8, p=0.014) (Fig. 2).

The univariate and multivariate logistic regression analyses were performed using possible confounding factors for presence of Cpc-PH in the dataset including HF type, HF duration, severe FMR, LV end-systolic dimension, LVEF, and LV diastolic dysfunction grade 3 (Table 5). The results of the univariate logistic regression analysis revealed that the presence of non-ischemic type cardiomyopathy was associated with decreased rate of Cpc-PH (OR: 0.49, 95% CI: 0.30–0.82, p=0.006). Severe FMR, increased LVESD, and LV diastolic dysfunction grade 3 were associated with Cpc-PH (OR: 2.26, 95% CI: 1.31–3.89, p=0.003; OR: 1.33, 95% CI: 1.01–1.77, p=0.034; and OR: 3.30, 95% CI: 1.74–6.24, p<0.001; respectively). The results of the multivariate logistic regression analysis revealed that the presence of LV diastolic dysfunction grade 3, severe FMR, and non-ischemic cardiomyopathy were associated with Cpc-PH independently from other confounding factors (OR: 3.21, 95% CI: 1.64–6.26, p<0.001; OR: 2.30, 95% CI: 1.25–4.26, p=0.008; and OR: 0.47, 95% CI: 0.27–0.83, p=0.009, respectively) (Table 5).

In Figures 3 and 4, we summarized the relative importance of each predictor in the model 1 (PVR) and model 2 (presence of Cpc-PH). In model 1, LV diastolic dysfunction grade 3 was ranked as the most important predictor and severe FMR was ranked as the second most important predictor for increased PVR. In model 2, LV diastolic dysfunction grade 3 was ranked as the most important predictor and severe FMR was ranked as the second most important predictor for presence of Cpc-PH.

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Table 4. Univariate and multivariate binary logistic regression analysis showing independent predictors of PVR ≥3 WU in candidates for HT

Variables	Univariate OR, 95% CI	*P*-value	Multivariate OR, 95% CI	*P*-value
Non-ischemic cardiomyopathy	0.52 (0.33-0.82)	0.004	0.56 (0.34-0.92)	0.023
HF duration	1.25 (0.94-1.69)	0.134	1.25 (0.91-1.74)	0.164
Severe FMR	2.27 (1.40-3.69)	<0.001	2.23 (1.30-3.82)	0.003
LVESD	1.37(1.07-1.75)	0.001	1.34 (0.99-1.82)	0.054
LVEF	0.79 (0.55-1.15)	0.231	1.01(0.61-1.67)	0.967
LVDD Grade 3	2.64 (1.51-4.61)	<0.001	2.45 (1.38-4.35)	0.002

CI - confidence interval; FMR - functional mitral regurgitation; HF - heart failure; HT - heart transplantation; LVDD - left ventricle diastolic dysfunction; LVEF - left ventricle ejection fraction; LVESD - left ventricle end-systolic dimension; OR - Odds ratio; PVR - pulmonary vascular resistance; WU - Wood unit

Table 5. Univariate and multivariate binary logistic regression analysis showing the independent predictors of the presence of Cpc-PH in candidates for HT

Variables	Univariate OR, 95% CI	*P*-value	Multivariate OR, 95% CI	*P*-value
Non-ischemic cardiomyopathy	0.49 (0.30-0.82)	0.006	0.47 (0.27-0.83)	0.009
HF duration	1.15 (0.82-1.61)	0.039	1.20 (0.82-1.76)	0.343
Severe FMR	2.26 (1.31-3.89)	0.003	2.30 (1.25-4.26)	0.008
LVESD	1.33 (1.01-1.77)	0.034	1.31 (0.92-1.86)	0.130
LVEF	0.76 (0.51-1.16)	0.201	0.89 (0.49-1.61)	0.695
LVDD Grade 3	3.30 (1.74-6.24)	<0.001	3.21 (1.64-6.26)	<0.001

CI - confidence interval; Cpc-PH - combined pre-post capillary pulmonary hypertension; FMR - functional mitral regurgitation; HF - heart failure; HT - heart transplantation; LVDD - left ventricle diastolic dysfunction; LVEF - left ventricle ejection fraction; LVESD - left ventricle end-systolic dimension; OR - Odds ratio

Discussion

Patients with severe FMR had a higher PVR value than those without severe FMR; severe FMR is the second most important risk factor for increased PVR; patients with severe FMR had a significantly increased rate of PVR ≥3 and PVR ≥5 WU; patients with severe FMR had more Cpc-PH; and severe FMR is the second most important risk factor for presence of Cpc-PH.

It is well known that severe mitral regurgitation increases PAPs. However, when previous studies are examined, it is seen that both primary and secondary valve pathologies were included in some, LVEF value was heterogeneous in some, and pulmonary pressures were measured non-invasively in most of them. In most of these studies, the definition of severe FMR and the definition of severe primary mitral insufficiency (EROA and RV value) were similar. In addition, there were a few studies including PVR measured using RHC. In this study, patients with HT were included (patient's clinics and LVEF were homogenous), new cutoff values at quantification of severe (FMR) and definition of PH were used, and invasive methods (rather than non-invasive) for hemodynamic measurements were performed.

This study showed that severe FMR increases PVR, PAPs, and PAWP value even at lower threshold, and severe FMR was the second most important risk factor for PVR independent from LV diastolic dysfunction, heart failure type, heart failure duration, LVEF, and LVESD. Cappola et al. (5) have determined that PAPm, mean systemic pressure, and PVR were the strongest predictors of mortality in patients with HT, and mortality rates nearly doubled with PVR ≥3 WU. Indeed, irreversible PH (PVR ≥5 despite vasodilators) was accepted as a contraindication for HT (2). In our study, rates of PVR ≥3 WU and PVR ≥5 WU were higher in patients with severe FMR. Although it is inconclusive whether treatment of severe FMR in patients with advanced heart failure will improve the outcome, it has been shown that it can reduce pulmonary pressures and PVR (21). Even treatment of severe FMR with ERO ≥0.4 cm^2 and RV ≥60 mL is controversial in these patients, it is very difficult to suggest to treat severe FMR at such a lower threshold. However, in patients with HT, the goal of the treatment can be to lower the PVR rather than reduce mortality. Because high PVR increases the rate of mortality in patients with HT, treatment strategies to decrease the PVR before transplantation, such as inotropes, vasodilators, sildenafil, and mechanical circulatory support, including LVAD, must be employed (1, 2, 22, 23). In some patients, these treatment methods may not be applicable or useful, and other methods, such as mitral valve repair or replacement, may be needed to reduce PVR for HT candidacy. Further studies can be designed to assess whether treatment of redefined severe FMR reduces pulmonary pressures and PVR. If treatment of severe FMR can be shown to reduce PVR, percutaneous or surgical treatment of severe FMR can then be tried as a bridge to candidacy for HT in patients with a high PVR.

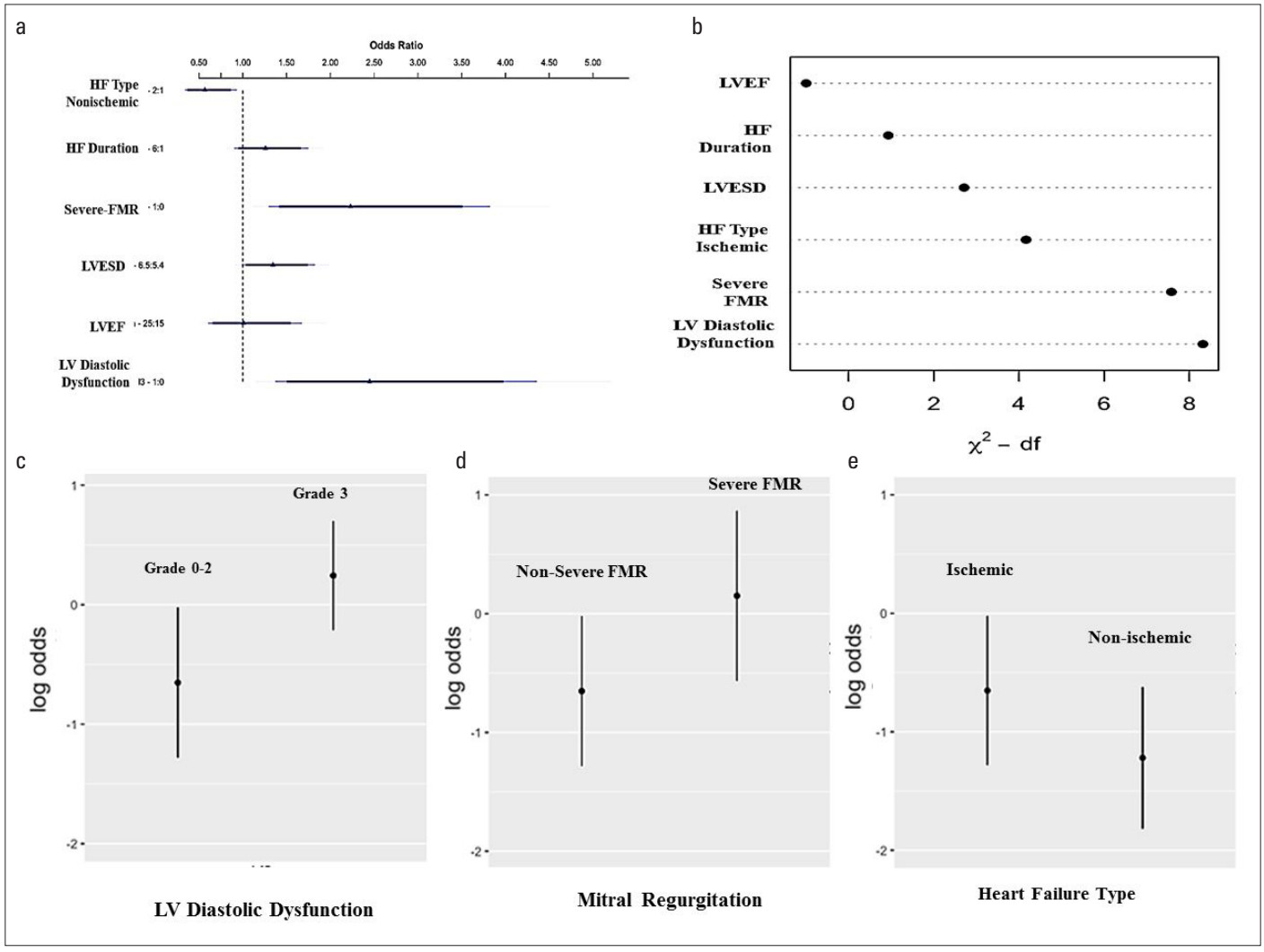

Figure 3. (a) Showing the Odds ratios of PVR ≥3 WU. The presence of nonischemic cardiomyopathy is associated with decreased PVR because 95% CI estimates <1. The presence of severe FMR or LV diastolic dysfunction is associated with increased PVR because their 95% CIs estimate >1. The HF duration, LVESD, and LVEF are not associated with increased risk of PVR because their CIs intersect one line. **(b)** Showing the importance of each predictor in the model (partial chi-square value of each predictor). The most two important predictors of increased PVR are LV diastolic dysfunction and severe FMR. **(c, d, e)** Showing the partial effect of the plot of LV diastolic dysfunction, FMR, and HF type

CI - confidence interval; df – difference; FMR - functional mitral regurgitation; HF - heart failure; LV - left ventricle; LVEF - left ventricle ejection fraction; LVESD - left ventricle end-systolic dimension; PVR - pulmonary vascular resistance; WU - Wood unit

The mean PVR value in our study was higher (4.0 WU) than that in previous studies, and this suggested that our patients had more advanced heart failure compared with those included in previous studies. Alexopoulos et al. (16) found that the PVR of patients with severe mitral regurgitation was 2.6 WU and was significantly higher than the PVR of patients with non-severe mitral regurgitation (17, 18). However, these patients had normal LV systolic function and primary mitral valve pathology. In a study examining the acute hemodynamic effect of percutaneous end-to-side mitral valve repair, it was determined that severe mitral regurgitation was related to increased PVR and mitral valve repair reduced PVR from 2.4 to 1.7 WU (24). However, in this study, the severity of LV dysfunction was lower than that of our patients (LVEF about 45%). Nishigawa et al. (25) determined that patients with severe FMR and end-stage heart failure had higher PVR values (2.3 WU) than normal, and it decreased after restrictive mitral ring annuloplasty (1.7 WU). However, in this study, the classification of FMR was based on EROA ≥0.4 cm^2 or RV ≥60 mL. In a study evaluating invasive hemodynamics of patients with cardiac transplant, without evaluating patients with mitral regurgitation as a separate group, pre-transplant PVR of patients was 2.6 WU. This value was lower than the PVR of our study patients with severe FMR but was similar to those without severe FMR (4).

The prevalence of PH and Cpc-PH in patients with heart failure depends on the population studied, the chronicity of disease, and the definition that was used (18, 26-28). In this study, the rate of Cpc-PH (42.9% of all patients) was higher than the rate of Cpc-PH in many previously published studies and reports (4, 26-30). This is due to several factors. First, our PH cutoff value was 20 mm Hg

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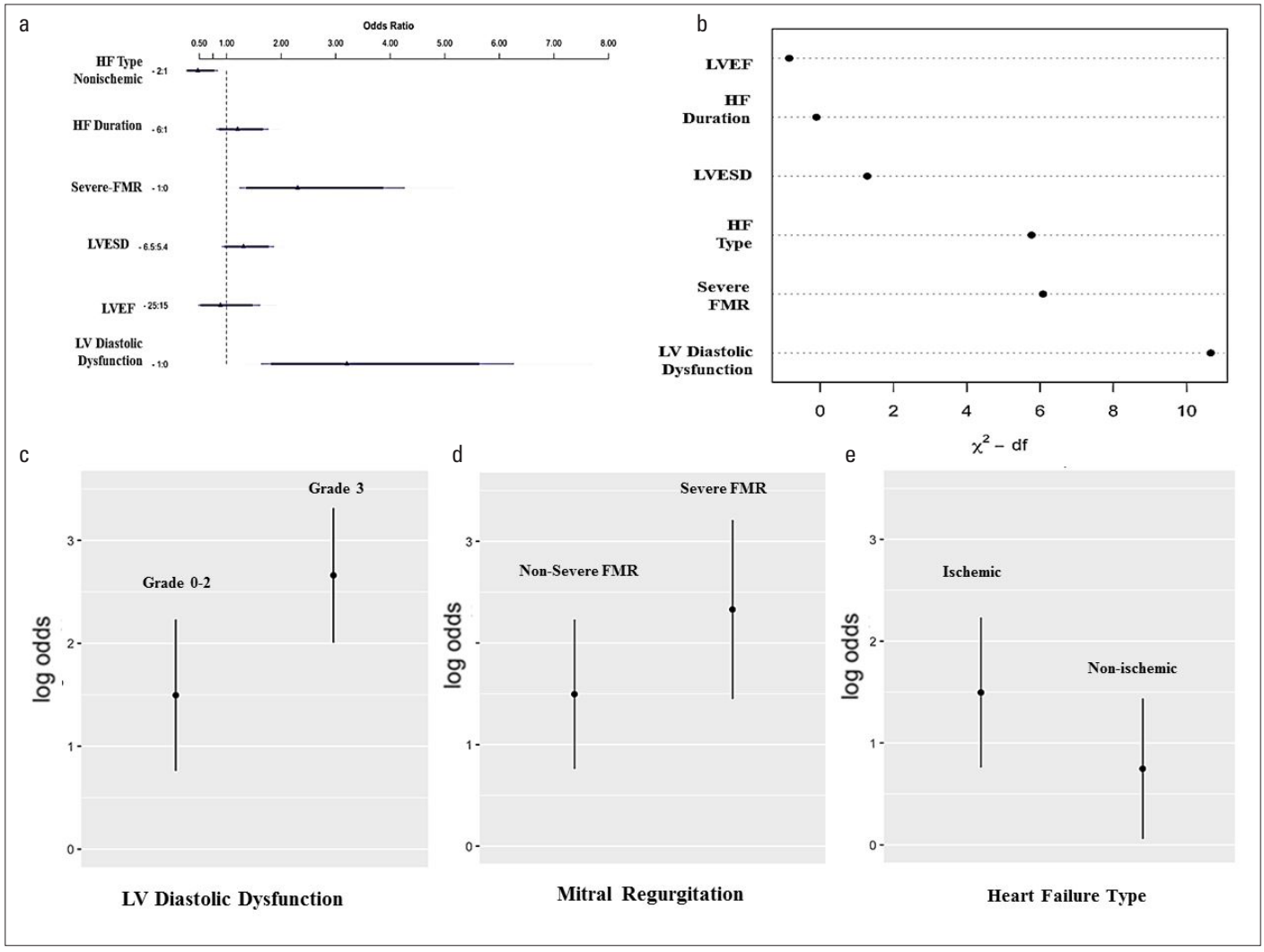

Figure 4. (a) Showing the odds ratios of the presence of Cpc-PH. The presence of nonischemic cardiomyopathy decreases the risk of the presence of Cpc-PH because 95% CI estimates <1. The presence of severe FMR or LV diastolic dysfunction increases the risk of Cpc-PH because their 95% CIs estimate >1. The HF duration, LVESD, and LVEF are not associated with Cpc-PH because their CIs intersect one line. **(b)** Showing the importance of each predictor in the model (partial chi-square value of each predictor). The most two important predictors of Cpc-PH are LV diastolic dysfunction and severe FMR. **(c, d, e)** Showing the partial effect of the plot of LV diastolic dysfunction, FMR, and HF type

CI - confidence interval; Cpc-PH - combined pre-post capillary pulmonary hypertension; df – difference; FMR - functional mitral regurgitation; HF - heart failure; LV - left ventricle; LVEF - left ventricular ejection fraction; LVESD - left ventricular end-systolic dimension

instead of 25 mm Hg, causing increased rate of PH diagnosis (both Ipc-PH and Cpc-PH). In addition, most of the previous studies had less advanced heart failure population. Most recently, Ghio et al. (4) have detected that the incidence of Cpc-PH in patients with HT was 32.2%, much lower than that in our study; however, they did not use the most recent definition of PH and did not have advanced HF patient population than our study. In this study, patients with severe FMR had more Cpc-PH than those without severe FMR (61.8% versus 40.7%). The LV diastolic dysfunction grade 3, severe FMR, and ischemic cardiomyopathy increased the rate of Cpc-PH. Severe FMR was the second most important risk factor for Cpc-PH independent from LV diastolic dysfunction, heart failure type, heart failure duration, LVEF, and LVESD.

Although there are many studies in the literature that have investigated the rate of Cpc-PH in patients with heart failure, to the best of our knowledge, there are only a few studies that examined the effect of severe FMR (based on the updated definition) on Cpc-PH in patients with advanced heart failure. In a study of patients with heart failure but in whom LVEF <30% was excluded, it was determined that severe FMR significantly increased the rate of Cpc-PH (26). It has been reported that patients with PH and mixed PH have a higher rate of severe mitral regurgitation than those without PH (28).

Study limitations

Although quantitative measurements were used for classification to differentiate severe FMR from moderate FMR, the patients with trace and mild regurgitation were visually classified as non-severe. Although we could not apply quantitative methods to these patients, it is very unlikely that this affected our results.

This study did not assess the effect of severe FMR on the outcomes of patients with and without PH. In previous studies, it has been shown that severe FMR was an independent risk factor for mortality in patients with moderate heart failure but not advanced heart failure (14, 15, 31). It is still uncertain whether severe FMR is an independent risk factor for mortality in patients with high PVR during end-stage heart failure. Further studies are needed to evaluate this effect.

Conclusion

Patients with severe FMR had higher PVR values than those without severe FMR. Severe FMR increases PVR, and it is an independent risk factor for higher PVR and presence of Cpc-PH in patients with HT even at lower cutoff values for FMR. Further studies are needed to discover whether treatment of severe FMR decreases the PVR value and allows patients who were disqualified for HT owing to high PVR to be HT candidates.

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