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Original Article / Özgün Makale

The effects of severe functional mitral regurgitation on right ventricular function in patients with advanced heart failure who were on waiting list for heart transplant

Kalp nakli için bekleme listesinde yer alan ileri kalp yetmezliği olan hastalarda ciddi fonksiyonel mitral yetersizliğinin sağ ventrikül fonksiyonuna etkileri

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ABSTRACT

Background: This study aims to investigate the effects of severe functional mitral regurgitation on the parameters that reflect right ventricular function such as tricuspid annular plane systolic excursion and right ventricular stroke work index in potential heart transplant recipients.

Methods: Between January 2015 and January 2017, a total of 282 consecutive patients (250 males, 32 females; mean age: 46±10 years; range, 18 to 66 years) with advanced heart failure who were referred for heart transplantation were retrospectively analyzed. The patients were divided into two groups as severe (n=84) and non-severe functional mitral regurgitation (n=198). Patients' medical histories, demographic characteristics, echocardiographic evaluations, and findings of right heart catheterization were recorded.

Results: The two groups were similar in terms of left ventricular ejection fraction, the New York Heart Association functional class, Interagency Registry for Mechanically Assisted Circulatory Support profile, and the duration of heart failure (p>0.05). Both groups were also similar with respect to tricuspid annular plane systolic excursion and right ventricular stroke work index. Functional mitral regurgitation was the only statistically significant variable in the univariate analysis for tricuspid annular plane systolic excursion (odds ratio [OR]: 0.58; 95% confidence interval [CI] 0.34-0.97; p=0.04), with no significant effect in the multivariate analysis. In the univariate analysis for right ventricular stroke work index, pulmonary arterial systolic pressure (OR: 0.77; 95% CI 0.67-0.88; p<0.001) was a significant variable and also had a significant effect in the multivariate analysis (OR: 0.92; 95% CI 0.87-0.97; p=0.003). In the tertile analyses, there were no significant differences between the two groups with respect to tricuspid annular plane systolic excursion and right ventricular stroke work index.

Conclusion: We found no significant difference in right ventricular functions between the severe and non-severe functional mitral regurgitation groups in patients with advanced heart failure who had relatively short follow-up. Right ventricle can maintain its normal function at early stage. Adaptive remodeling of right ventricle may have an effect on these findings. Severe functional mitral regurgitation may be associated with adverse effects on advanced heart failure by increasing the right ventricular afterload.

Keywords: Advanced heart failure, functional mitral regurgitation, right ventricular function.

ÖZ

Amaç: Bu çalışmada, olası kalp nakli alıcılarında şiddetli fonksiyonel mitral yetersizliğin triküspit anüler düzlem sistolik ekskürsiyonu ve sağ ventrikül atım işi indeksi gibi sağ ventrikül fonksiyonunu yansıtan parametreler üzerindeki etkileri araştırıldı.

Çalışma planı: Ocak 2015 - Ocak 2017 tarihleri arasında, kalp nakli için sevk edilen ileri kalp yetmezliği olan toplam 282 ardışık hasta (250 erkek, 32 kadın; ort. yaş: 46±10 yıl; dağılım, 18-66 yıl) retrospektif olarak incelendi. Hastalar ciddi (n=84) ve ciddi olmayan fonksiyonel mitral yetersizlik (n=198) olmak üzere iki gruba ayrıldı. Hastaların tıbbi öyküleri, demografik özellikleri, ekokardiyografik değerlendirmeleri ve sağ kalp kateterizasyon bulguları kaydedildi.

Bulgular: İki grup da sol ventrikül ejeksiyon fraksiyonu, New York Kalp Derneği fonksiyonel sınıfı, Mekanik Dolaşım Destek Cihazları Kurumlararası Kayıt sistemi profili ve kalp yetmezliği süresi açısından benzerdi (p>0.05). Her iki grup da, triküspit anüler düzlem sistolik ekskürsiyonu ve sağ ventrikül atım işi indeksi açısından da benzerdi. Fonksiyonel mitral yetersizlik, triküspit anüler düzlem sistolik ekskürsiyonu için yapılan tek değişkenli analizde tek istatistiksel olarak anlamlı değişkendi (olasılık oranı [OR]: 0.58; %95 güven aralığı [CI] 0.34-0.97; p=0.04) ve çok değişkenli analizde anlamlı bir etkisi gözlenmedi. Sağ ventrikül atım işi indeksi için yapılan tek değişkenli analizde, pulmoner arter sistolik basıncı (OR: 0.77; %95 CI 0.67-0.88; p<0.001) tek anlamlı değişken olup, çok değişkenli analizde de anlamlı bir etkisi vardı (OR: 0.92; %95 CI 0.87-0.97; p=0.003). Tertil analizlerinde iki grup arasında triküspit anüler düzlem sistolik ekskürsiyonu ve sağ ventrikül atım işi indeksi açısından anlamlı bir fark yoktu.

Sonuç: Nispeten kısa takip süresi olan ileri kalp yetmezliği olan hastalarda ciddi ve ciddi olmayan fonksiyonel mitral yetersizlik grupları arasında sağ ventrikül fonksiyonları açısından anlamlı bir fark izlenmedi. Sağ ventrikül, erken evrede normal fonksiyonlarını sürdürebilir. Sağ ventrikülün adaptif bir şekilde yeniden modellenmesinin bu sonuçlar üzerinde etkisi olabilir. Ciddi fonksiyonel mitral yetersizlik, sağ ventrikül art yükünü artırarak ileri kalp yetmezliği üzerinde olumsuz etkiler ile ilişkili olabilir.

Anahtar sözcükler: İleri kalp yetmezliği, fonksiyonel mitral yetersizlik, sağ ventrikül fonksiyonu.

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Patients with advanced heart failure (AdHF) account for approximately 1 to 10% of the overall population with heart failure (HF).[1-3] It is a challenging condition due to severe persistent clinical symptoms refractory to standard medical treatments, with high incidences of re-hospitalization and mortality. Patients with AdHF refractory to medical treatment often require further interventions, including mechanical circulatory support (MCS) and heart transplantation.[4]

Right ventricular (RV) dysfunction has adverse effects on the course of disease and mortality in the presence of chronic HF. Several parameters contribute to RV dysfunction including a longer duration of HF, pulmonary hypertension which as defined by a mean pulmonary artery pressure (PAPm) ≥25 mmHg regardless of the cause, and increased pulmonary vascular resistance (PVR) which, in turn, lead to elevated right-sided filling pressures in patients with HF.[5,6] Moreover, the presence of RV dysfunction may have an adverse effect on eligibility of patients for further therapies. Therefore, RV function must be taken into account in the pre-transplant evaluation.[7]

Echocardiography is the first-choice imaging technique to evaluate RV function. Tricuspid annular plane systolic excursion (TAPSE) is a straightforward and practical parameter for RV function.[8] Echocardiographic evaluation of the RV can be challenging due to its complex geometrical structure, resulting in inaccurate assessments, as well as considerable interobserver variability.

Right heart catheterization (RHC) still remains to be the gold standard to assess RV function, particularly for patients awaiting assist device implantation or transplantation. In addition, the guidelines of the International Society for Heart and Lung Transplantation (ISHLT) recommend serial RHC at three-month intervals in heart transplant candidates.[9] Right ventricular stroke work index (RVSWI) is one of the parameters of RHC to assess RV function, while PVR, pulmonary arterial elastance (PaE), pulmonary arterial capacitance (PaC) provide information on pulmonary afterload, the evaluation of which is as significant as that of RV function in patients with AdHF.[10-13]

Functional mitral regurgitation (FMR) is secondary to left ventricular (LV) remodeling without organic mitral valve disease. It has additive effects on LV filling and pulmonary arterial pressures in patients with HF.[14]

In the present study, we aimed to investigate the effects of severe FMR on the echocardiographic and RHC parameters such as TAPSE and RVSWI among potential heart transplant recipients.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Kartal Koşuyolu High Specialization Training and Research Hospital, Department of Cardiology between January 2015 and January 2017. A total of 368 consecutive patients with AdHF who were referred for heart transplantation were screened. Patients with AdHF who had no obvious contraindications for heart transplantation were evaluated at the Transplantation Council regardless of their New York Heart Association (NYHA) functional classes. Patients with NYHA Class I-II were treated medically and followed by members of the Transplantation Council. Demographic characteristics, cardiovascular risk factors, comorbidities, the NYHA functional class, the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile, and echocardiographic and catheterization findings were recorded. Only patients who underwent echocardiography before RHC on the same day were included in the study. Inclusion criteria were a left ventricular ejection fraction (LVEF) ≤25% and age ≥18 years. Exclusion criteria were primary mitral and tricuspid valve pathology, prior valvular surgery, severe aortic regurgitation or stenosis; prior RV myocardial infarction; age ≥70 years; inotropic dependency, the need for intra-aortic balloon pump; multiorgan failure; infiltrative, constrictive, or hypertrophic cardiomyopathy; congenital heart disease; connective tissue disease; a history of moderate or severe chronic obstructive pulmonary disease or primary lung disease; a serum creatinine level of ≥2.5 mg/dL and comorbidities causing contraindication as determined by the ISHLT guidelines for heart transplantation. Finally, a total of 282 patients (250 males, 32 females; mean age: 46±10 years; range, 18 to 66 years) were included in the study (Figure 1). The patients were divided into two groups as severe FMR (n=84) and non-severe FMR (n=198).

Echocardiographic variables

Echocardiographic evaluation of patients was made according to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the echocardiographic assessment of the right heart.[8] The LVEF was determined by the biplane Simpson's method. The following parameters were measured: the sizes of the left atrium (LA), LV

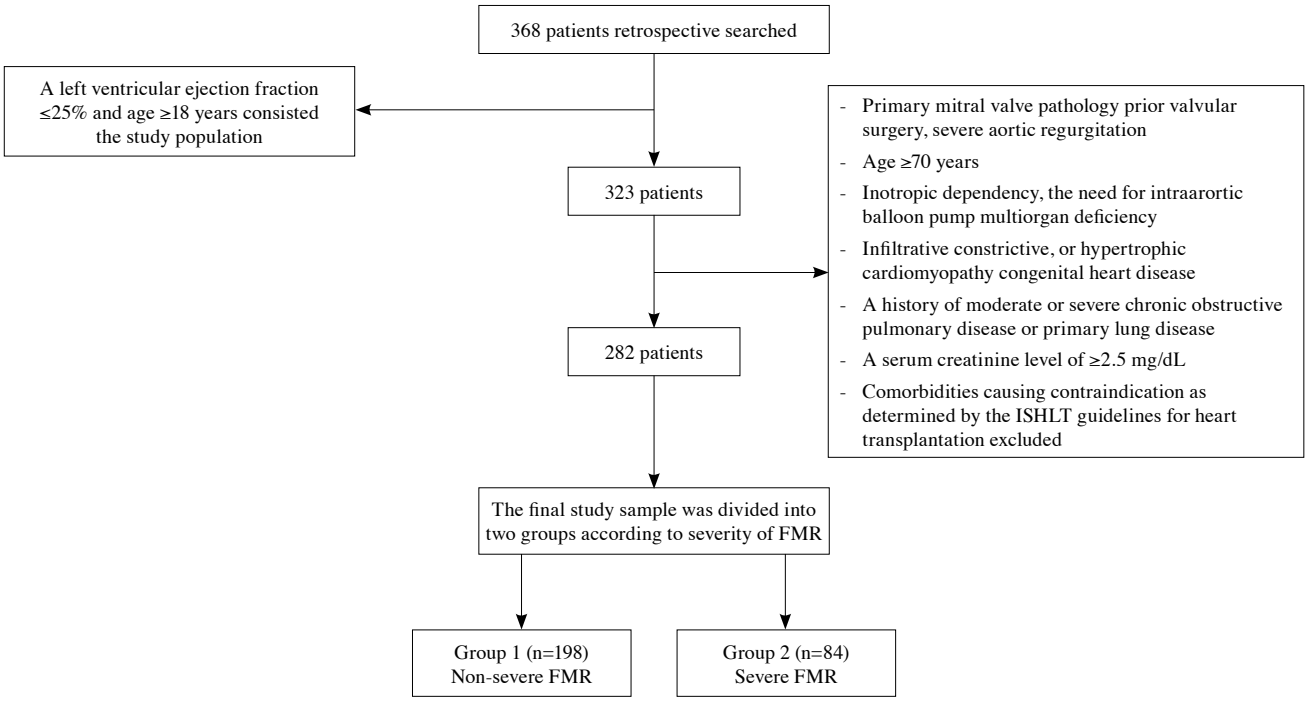

Figure 1. CONSORT diagram of study population.
FMR: Functional mitral regurgitation; ISHLT: The International Society for Heart and Lung Transplantation.

and RV, the ratio of early transmitral flow velocity (E)-to-early diastolic mitral annular velocity (e') and deceleration time (DT) of the mitral E wave, pulmonary arterial systolic pressure (PAPs), PVR, TAPSE, systolic tricuspid velocity, and plethora. To differentiate severe FMR from moderate FMR, the effective regurgitant orifice area (EROA) and regurgitant volume (RV') were calculated using the proximal isovelocity surface area (PISA) method. Severe FMR was defined as an EROA of ≥20 mm^2 and an RV of ≥30 mL.[15-17] In addition, FMR was evaluated with PISA measurement in 146 patients (70 of whom with severe, 76 of whom with moderate FMR) and also by conventional methods, such as vena contracta (VC) and visual classification; in the presence of inconsistent results between the methods, the visual classification results were taken into account. The PISA could not be measured in 136 patients, most of whom (82%) had mild and mild-to-moderate FMR and, thus, FMR was visually classified as non-severe FMR. Of 136 patients, 18% had moderate and severe FMR on the basis of visual classification, and due to eccentric and wall impinging jet, PISA could not be measured. To differentiate between severe FMR and moderate FMR, VC and a pulmonary vein flow pattern through transesophageal echocardiography were assessed. Systolic flow reversal in the pulmonary vein and a VC ≥0.7 cm was defined as a severe FMR. Tricuspid regurgitation (TR) was evaluated with color flow Doppler and a TR VC ≥0.7 cm was recognized as severe TR. The PAPs was calculated using TR velocity plus RA pressure (4 × [peak systolic TR velocity at end-expiration]2 + RA pressure). The RA pressure was estimated from inferior vena cava (IVC) and its collapsibility. The IVC diameter <2.1 cm that collapsed >50% with a sniff suggested a normal RA pressure (5 mmHg), IVC diameter >2.1 cm that collapsed <50% with a sniff suggested an elevated RA pressure (15 mmHg) and IVC diameters >2.1 cm without collapse (<50%), RA pressure was upgraded to 20 mmHg. When uncertainty existed, secondary findings of elevated RA pressure were assessed.

Hemodynamic variables

Right heart catheterization was performed using a Swan-Ganz catheter and LV and aortic pressures were assessed using a pigtail catheter under hemodynamic and fluoroscopic guidance according to the 2015 European Society of Cardiology/ European Respiratory Society (ESC/ERS) guidelines

for the diagnosis and treatment of pulmonary hypertension.[9] Pulmonary arterial systolic, mean and diastolic pressures (PAPs, PAPm, PAPd), pulmonary capillary wedge pressure (PCWP), mean right atrial pressure (RAPm), transpulmonary pressure gradient (TPG), diastolic pulmonary gradient (DPG), PVR, PaE [PaE= (PAPm-PCWP)/SV], PaC [PaC= SV/(PAPs-PAPd)], RVSWI [RVSWI= (PAPm-RAPm)×SVI×0.0136], systolic blood pressure (SBP) and diastolic blood pressure (DBP), LV end-diastolic pressure (LVEDP), transsystemic gradient (TSG), systemic vascular resistance (SVR), cardiac output (CO) by the direct Fick method, cardiac index (CI), stroke volume (SV), stroke volume index (SVI) and left ventricle stroke work index [LVSWI = (mean aortic pressure-PAWP)×SVI×0.0136] were measured.

RV functional analysis

The RV function was evaluated using both echocardiographic and RHC parameters. A TAPSE of >2.0 cm suggests normal biventricular function, while a TAPSE of ≤1.5 cm suggests RV dysfunction according to the ACC/AHA guidelines for the echocardiographic assessment of the right heart in adults.[8,18] The cut-off value of RVSWI in patients with AdHF has not been reported, while the normal range of RVSWI for healthy individuals is considered to be 5 to 10 g×m/m^2/beat. Some previous studies have shown that an RVSWI of <5 g×m/m^2/beat reflects RV dysfunction.[19,20] In this study, RV dysfunction was defined as a TAPSE of ≤1.5 cm and an RVSWI of <5 g×m/m^2/beat.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were presented in mean ± standard deviation (SD) or median (interquartile range [IQR]), while categorical variables were presented in number and frequency. The two groups were compared using the Student t-test or Wilcoxon rank-sum test for continuous variables and Fisher exact test for categorical variables. Multivariate logistic regression models were used to analyze the data. In the multivariate analysis, covariates such as severe FMR, PAP, PVR, LVEF, and the duration of HF were identified according to their clinical and biological plausibility and in association with RV dysfunction which was shown in previous studies.[5,9,10,14,15] We also performed univariate analysis and, then, variables with a p value of <0.10 were included in the multivariate model. Tertile analyses were made according to TAPSE and RVSWI. A two-tailed *p* value of <0.05 was considered statistically significant.

RESULTS

Patient characteristics

The baseline demographic, clinical and laboratory characteristics of the two patient groups are shown in Table 1. The patients were divided into two groups as severe FMR and non-severe FMR. Both groups were similar with respect to body mass index, hypertension, diabetes, hyperlipidemia, smoking status, prior coronary arterial bypass grafting, prior percutaneous coronary intervention, chronic obstructive pulmonary disease, peripheral arterial disease, atrial fibrillation, and the duration and etiology of HF. There was no history of cerebrovascular disease in the severe FMR group, while 10 patients in the non-severe FMR group had cerebrovascular disease (p=0.03). Most patients were in the NYHA Class III-IV and the INTERMACS profile 5-6, with no significant differences in the subgroups of the NYHA functional classes (p=0.47) or the INTERMACS profiles (p=0.25). Although patients with severe FMR had lower hemoglobin and higher albumin levels (p=0.01 for both), the levels of blood urea nitrogen, creatinine, sodium and total bilirubin were similar between the two groups.

Echocardiographic findings

Echocardiographic parameters are shown in Table 2. There was no significant difference in the LVEF between the two groups (p=0.44). The LA diameter, LV end-diastolic diameter and LV end-systolic diameter were found to be higher in patients with severe FMR, compared to those with non-severe FMR (p<0.01). Although higher PAPs and PVR and a higher incidence of severe TR were found in patients with severe FMR (p<0.01, p<0.01, p=0.01, respectively), TAPSE and ST (systolic velocity of the tricuspid annulus) which reflect RV function were similar in both groups (p=0.57, p=0.91).

Hemodynamic characteristics

Findings of left and RHC are shown in Table 3. Patients with severe FMR had significantly lower CO, CI, SV, SVI, and LVSWI (p=0.04, p=0.04, p=0.01, p<0.01, p<0.01, respectively). Systemic vascular resistance was similar in the two groups (p=0.81). Patients with severe FMR had significantly increased PAPs, PAPm, PAPd, PCWP, and TPG (p=0.01, p<0.01, p<0.01, p=0.04 and p=0.01,

Table 1. Baseline characteristics of the patients

	Non-severe FMR (n=198)			Severe FMR (n=84)			
Variables	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			46.5±10.0			45.7±11.5	0.58
Sex							
Male	174	87.9		76	90.5		0.53
Body mass index (kg/m^2)			27.3±19.2			26.1±5.3	1.3
Hypertension	62	31.3		18	21.4		0.09
Diabetes	51	25.8		17	20.2		0.32
Hyperlipidemia	54	27.3		22	26.2		0.85
Obesity	33	16.7		18	21.4		0.34
Smoking status	94	47.5		37	44		0.59
Prior PCI	66	33.3		25	29.8		0.55
Prior CABG	33	16.7		13	15.5		0.80
Cerebrovascular disease	10	5.1		0	0		0.03
COPD	10	5.1		4	4.8		0.91
Peripheral arterial disease	11	5.6		2	2.4		0.24
Atrial fibrillation	32	16.2		8	9.5		0.14
The duration of heart failure (month)			4.4±4.0			4.3±4.0	0.88
The etiology of heart failure							0.45
Ischemic	98	49.4		100	45		
Nonischemic	37	45.1		50.5	54.8		
ICD	84	42.4		27	32.2		0.10
CRT	14	7.1		6	7.2		0.96
NYHA functional class							0.47
I	9	4.5		7	8.5		
II	52	26.2		19	23.1		
III	79	39.8		33	40.2		
IV	58	29.3		23	28		
INTERMACS profile							0.25
1	6	3		2	2.4		
2	5	2.5		4	4.8		
3	11	5.6		6	7.1		
4	26	13.1		13	15.5		
5	50	25.3		22	26.2		
6	65	32.8		25	29.8		
7	35	17.7		12	19.3		
Hemoglobin (g/dL)			13.2±2.2			12.2±1.8	0.01
Blood urea nitrogen (mg/dL)			50.0±28.6			52.0±32.7	0.65
Creatinine (mg/dL)			1.16±0.7			1.37±1.1	0.30
Sodium (mEq/L)			136.1±4.0			135.0±4.7	0.06
Albumin (mg/dL)			3.89±0.6			3.98 ±0.6	0.01
Total bilirubin (mg/dL)			1.66±1.5			1.35±1.5	0.84

FMR: Functional mitral regurgitation; SD: Standard deviation; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; COPD: Chronic obstructive pulmonary disease; ICD: Implantable cardioverter defibrillator; CRT: Cardiac resynchronization therapy; NYHA: New York Heart Association; INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support.

Table 2. Echocardiographic parameters

	Non-severe FMR			Severe FMR			
Variables	n	%	Mean±SD	n	%	Mean±SD	*p*
LVEF (%)			20.4±4.2			20.0±3.9	0.44
LVEDD (cm)			6.6±0.9			7.2±0.9	<0.01
LVESD (cm)			5.7±1.0			6.3±0.9	<0.01
LAD (cm)			4.6±0.7			5.1±0.8	<0.01
MV DT (msec)			122.7±43			114±30.6	0.13
MV E/E'			14.7±5.0			16.8±5.8	0.01
MV EROA (mm^2)			0.16±0.4			0.34±0.11	<0.01
MV RV' (mL)			19.8±5.0			42.1±15.1	<0.01
Severe tricuspid regurgitation	40	20.4		28	30.1		0.01
PAPs (mmHg)			43.5±16.0			52.0±13.0	<0.01
PVR (Wood units)			3.9±1.8			4.1±1.9	<0.01
TAPSE (cm)			1.47±0.5			1.61±0.5	0.57
ST (cm/sec)			9.4±2.7			9.3±2.1	0.91
Plethora	45	26.6		19	23.8		0.68

FMR: Functional mitral regurgitation; SD: Standard deviation; LVEF: Left ventricular ejection fraction; LVEDD: Left ventricle end-diastolic diameter; LVESD: Left ventricle end-systolic diameter; LAD: Left atrial diameter; MV: Mitral valve; DT: deceleration time; EROA: Effective regurgitant orifice area; RV': Regurgitant volume; PAPs: Pulmonary arterial pressure systolic; PVR: Pulmonary vascular resistance; TAPSE: Tricuspid annular plane systolic excursion; ST: Systolic velocity of the tricuspid annulus.

Table 3. Findings of left and right heart catheterization

	Non-severe FMR	Severe FMR	
Variables	Mean±SD	Mean±SD	*p*
Cardiac output (L/min)	3.42±1.0	3.23±0.9	0.04
Cardiac index (L/min/m^2)	1.86±0.5	1.71±0.4	0.04
Stroke volume (mL/beat)	42.7±15.4	37.7±10.1	0.01
Stroke volume index (mL/beat/m^2)	22.9±8.9	19.9±5.2	<0.01
LVSWI (g×m/m^2/beat)	16.6±11.2	12.5±6.6	<0.01
SVR (WU)	21.8±7.7	22.0±8.9	0.81
Pulmonary arterial pressure, systolic (mmHg)	50.3.±17.6	57.5±15.6	0.01
Pulmonary arterial pressure, mean (mmHg)	31.9±11.2	37.4±10.3	<0.01
Pulmonary arterial pressure, diastolic (mmHg)	21.2±9.1	25.3±8.7	<0.01
TPG (mmHg)	10.2±7.4	13.5±7.8	0.01
PCWP (mmHg)	21.8±7.4	24.6±7.3	0.04
Right atrial pressure (mmHg)	11.1±6.5	12.1±5.8	0.19
PVR (WU)	3.3±2.9	4.4±2.6	0.02
RVSWI (g×m/m^2/beat)	9.8±3.7	10.1±3.3	0.44
PaC	1.8±1.0	1.3±0.7	<0.01
PaE	1.28±0.6	1.7±0.7	<0.01

FMR: Functional mitral regurgitation; SD: Standard deviation; LVSWI: Left ventricle stroke work index; SVR: Systemic vascular resistance; TPG: Transpulmonary pressure gradient; PCWP: Pulmonary capillary wedge pressure; PVR: Pulmonary vascular resistance; RVSWI: Right ventricle stroke work index, PaC: Pulmonary arterial capacitance; PaE: Pulmonary arterial elastance.

Table 4. Univariate and multivariate analyses for TAPSE

	Univariable analysis		
Variables	Odds ratio	95% CI	*p*
Severe FMR	0.58	0.34-0.97	0.04
Pulmonary arterial pressure-systolic (mmHg)	0.99	0.98-1.00	0.42
Pulmonary arterial pressure-mean (mmHg)	0.99	0.98-1.00	0.23
Pulmonary arterial pressure-diastolic (mmHg)	0.99	0.97-1.02	0.47
PVR (WU)	1.03	0.94-1.11	0.56
LVEF (%)	0.98	0.92-1.03	0.41
The duration of heart failure (month)	1.04	0.98-1.10	0.26

TAPSE: Tricuspid annular plane systolic excursion; CI: Confidence interval; FMR: Functional mitral regurgitation; PVR: Pulmonary vascular resistance; LVEF: Left ventricular ejection fraction.

respectively). Severe FMR was associated with an increased PVR, PaE and a decreased PaC (p=0.02, p<0.01, p<0.01, respectively), but not with RVSWI (p=0.44).

Univariate and multivariate analyses for TAPSE and RVSWI

Univariate and multivariate analysis results for TAPSE are shown in Table 4. The presence of a TAPSE of ≤1.5 cm and an RVSWI of <5 g×m/m^2/beat was accepted as RV dysfunction.[8,18-20] Accordingly, multivariate logistic regression analysis was performed to identify RV dysfunction. In addition, PAPs, PAPd, PVR, LVEF and the duration of HF were included in the multivariate analysis. The only statistically significant variable in the univariate logistic regression analysis for TAPSE was severe FMR (odds ratio [OR]: 0.58; 95% confidence interval [CI] 0.34-0.97; p=0.04) and, therefore, we did not perform multivariate analysis for TAPSE.

Both univariate and multivariate regression analysis results for RVSWI are shown in Table 5. In the univariate logistic regression analysis for RVSWI, PAPs (OR: 0.77; 95% CI 0.67-0.88; p<0.001), PAPm (OR: 0.74; 95% CI 0.63-0.85; p<0.001), PAPd (OR: 0.67; 95% CI 0.55-0.83; p<0.001), and PVR (OR: 0.38; 95% CI 0.20-0.75; p=0.005) were significant variables, while PAPs (OR: 0.95; 95% CI 0.92-0.98; p<0.001) also had a significant effect in the multivariate logistic regression analysis and PAPm was not included in the multivariate study due to collinearity.

The tertile analyses according to TAPSE and RVSWI

Table 6 shows TAPSE tertiles in patients with severe and non-severe FMR. In the light of previous studies, the patients were classified into three tertiles according to TAPSE and RVSWI.[8,18-21] The TAPSE tertiles were defined as low (TAPSE ≤1.5 cm), middle

Table 5. Univariate and multivariate analyses for RVSWI

	Univariable analysis			Multivariable analysis		
Variables	Odds ratio	95% CI	*p*	Odds ratio	95% CI	*p*
Severe FMR	0.58	0.12-2.80	0.50	_	_	_
Pulmonary arterial pressure-systolic (mmHg)	0.77	0.67-0.88	<0.001	0.95	0.92-0.98	<0.001
Pulmonary arterial pressure-mean (mmHg)	0.74	0.63-0.85	<0.001	_	_	_
Pulmonary arterial pressure-diastolic (mmHg)	0.67	0.55-0.83	<0.001	1.001	0.95 -1.05	0.97
PVR (WU)	0.38	0.20-0.75	0.005	1.04	0.96-1.12	0.34
LVEF (%)	1.08	0.91-1.28	0.36	_	_	_
The duration of heart failure (month)	0.98	0.83-1.16	0.84	_	_	_

RVSWI: Right ventricular stroke work index; CI: Confidence interval; FMR: Functional mitral regurgitation; PVR: Pulmonary vascular resistance; LVEF: Left ventricular ejection fraction.

Table 6. TAPSE tertiles in patients with severe and non-severe FMR

	Non-severe FMR (n=198)		Severe FMR n=84)		
Variables	n	%	n	%	*p*
TAPSE ≤1.5 cm	97	48.9	38	46.3	0.56
TAPSE 1.6-1.9 cm	68	34.3	33	40.2	0.42
TAPSE ≥2.0 cm	33	16.6	11	13.4	0.35

FMR: Functional mitral regurgitation; TAPSE: Tricuspid annular plane systolic excursion.

Table 7. RVSWI tertiles in patients with severe and non-severe FMR

	Non-severe FMR (n=198)		Severe FMR n=84)		
Variables	n	%	n	%	*p*
RVSWI <5 (gxm/m^2/beat)	68	34.3	18	21.9	0.05
RVSWI 5-10 (gxm/m^2/beat)	101	51	51	62.1	0.13
RVSWI >10 (gxm/m^2/beat)	29	14.6	13	15.8	0.85

FMR: Functional mitral regurgitation; RVSWI: Right ventricle stroke work index.

(1.6-1.9 cm), high (TAPSE ≥2.0 cm). In the severe FMR group, 40 (44.4%) patients, 37 (41.1%) patients, and 13 (14.4%) patients fell into the low, middle, and high TAPSE tertiles, respectively.

Table 7 shows RVSWI tertiles in patients with severe and non-severe FMR. Similarly, the patients were classified into three RVSWI tertiles (low: RVSWI <5 g×m/m^2/beat; middle: RVSWI 5-10 g×m/m^2/beat; high: RVSWI >10 g×m/m^2/beat). In the severe FMR group, 14 (20.3%) patients were in the low RVSWI tertile, 41 (59.4%) patients were in the middle RVSWI tertile, and 14 (20.3%) patients were in the high RVSWI tertile. There were no significant differences between the two FMR groups with respect to the TAPSE (p=0.56, p=0.42, p=0.35, respectively) and RVSWI (p=0.05, p=0.13, p=0.85, respectively) tertiles.

DISCUSSION

We found no significant differences between the non-severe FMR and severe FMR groups in terms of TAPSE and RVSWI, reflecting the right heart systolic function. In addition, there were no significant differences in TAPSE and RVSWI between the two FMR groups in the univariate, multivariate, and tertile analyses. The patients with severe FMR had significantly higher PVR, PaE and significantly lower PaC than the patients with non-severe FMR. The severe FMR group had also higher PAPs, PAPm and PAPd, as well as increased PCWP and decreased CO, CI, SV, SVI and LVSWI, as expected.

Advanced heart failure represents the last phase of HF. Standard treatments are frequently inadequate; heart transplantation and MCS devices are potential treatment options in selected patients. Right ventricular dysfunction is a significant parameter for the selection of patients. We examined the effect of FMR on RV function which is an important comorbidity in patients with AdHF. We found no significant differences between the non-severe FMR and severe FMR groups in terms of TAPSE and RVSWI, reflecting the right heart systolic function (p=0.57, p=0.44, respectively). Although there were no significant differences in TAPSE and RVSWI between the two FMR groups in the univariate, multivariate and tertile analyses, the patients with severe FMR had significantly higher PVR, PaE and significantly lower PaC than the patients with non-severe FMR (p=0.01, p=0.02, p<0.01, respectively). The severe FMR group had also higher PAPs, PAPm and PAPd, as well as increased PCWP and decreased CO, CI, SV, SVI and LVSWI, as expected. The only statistically significant variable in the univariate logistic regression analysis for TAPSE was severe FMR. In the univariate logistic regression analysis for RVSWI, PAPs, PAPd, and PVR were significant variables, while PAPs had also a significant effect in the multivariate analysis.

Previous studies have shown that AdHF accompanied by severe FMR is associated with dyspnea, exercise intolerance, and an increased risk for mortality due to increased pulmonary pressures.[14,22,23] Cappola et al.[24] reported that PAPm and PVR were the strongest predictors of mortality, with mortality rates almost doubled when PVR was ≥3 WU. In our study, the mean PAPm was 37.4±10.3 mmHg and the mean PVR was 4.4±2.6 WU and significantly increased PAPm and PVR were found in the severe FMR group, indicating the negative effects of severe FMR on PAP and PVR in heart transplant candidates.

Nishikawa and Tanemoto[25] showed that an increased PVR of 2.3 WU in patients with AdHF accompanied by severe FMR decreased to 1.7 WU after mitral annuloplasty. Another study reported significant improvements in ejection fraction (EF) and the NYHA functional class after mitral valve repair or replacement surgery, as well as significant decreases in PAPs and PCWP among patients with an EF <35% and severe FMR.[26] The authors speculated that a surgery for secondary MR in selected patients with a low EF could be an alternative to cardiac transplantation. A retrospective study on MitraClip® treatment in patients with AdHF found decreased PAP and PVR and improvements in the NYHA functional class and reported that MitraClip® treatment might be beneficial as a bridge-to-transplant in patients on the transplantation list.[27] There were also some case reports where MitraClip® treatment was found to be effective in patients with severe FMR, resulting in removal from the waiting list for transplantation.[28,29]

Many hemodynamic parameters reflecting pulmonary vascular remodeling have been studied, one of which is PVR though its relationship with CO limits its diagnostic value. New parameters such as PaC and PaE have been proposed, as PVR may be higher in patients with a low CO. While PVR reflects the resistive component of the RV afterload, PaC reflects its dynamic component.[30] Dragu et al.[11] found that PaC was a strong independent hemodynamic marker in HF and could contribute to increased mortality rates associated with reactive pulmonary hypertension (PAH). In addition, several studies have reported that, for the assessment of RV afterload, evaluating PVR together with PaC may be more appropriate than evaluating these two parameters separately.[11,12,31] Amin et al.[13] proposed that, in addition to PVR, PaE calculation might be useful to recognize the changes in the RV afterload early and precisely. We also assessed RV afterload along with PVR, PaE, and PaC and found that PaC was significantly lower in the severe FMR group, while PVR and PaE were significantly higher.

In this study, RV afterload which was defined by PCWP, was significantly increased in patients with severe FMR, but RV function was similar in the two groups, which can be explained with adaptive remodeling of the RV due to RV-pulmonary artery coupling which is defined as the RV adaptation to chronic overload. Our patient group consisted of patients diagnosed with HF within a maximum of four years. The RV function would be preserved at the early stage of overload, but maladaptation may occur over time, resulting in RV dysfunction. Therefore, despite the increased pulmonary afterload, RV function could appear normal in early stage of the disease.

This study has some limitations. It is a retrospective study presenting a single tertiary center experience; therefore, the study cohort may not represent the overall AdHF population. While quantitative measurements were used for classification to differentiate severe FMR from moderate FMR, mild and mild-to-moderate mitral regurgitation were visually classified as non-severe FMR, since PISA could not be measured in most patients. Proportionate versus disproportionate mitral regurgitation could not be evaluated due to the absence of end-diastolic volume measurements. As no prognostic data were available, we could not assess the relationship of mitral regurgitation and RV dysfunction with prognosis. Similarly, as the duration of mitral regurgitation was unavailable, its effect on our results could not be identified. Although conditions that directly affect primarily RV were excluded, RV could not have been assessed with cardiac magnetic resonance imaging to evaluate intrinsic RV dysfunction. Of note, the present study was performed before amendments in the criteria of pulmonary hypertension; therefore, we used a PABm of >25 mmHg to define pulmonary hypertension.

In conclusion, right ventricular function as assessed by the right ventricular stroke work index and tricuspid annular plane systolic excursion was similar between the patients with severe and non-severe functional mitral regurgitation. However, the patients with severe functional mitral regurgitation had significantly higher pulmonary afterload as assessed by pulmonary vascular resistance, pulmonary arterial capacitance, and pulmonary arterial elastance. Given that the relatively short follow-up of the patients with advanced heart failure (approximately eight months), it can be speculated that right ventricular function, which appeared to be preserved at an early stage,

may worsen in the presence of an increased afterload over time due to constant pressure overload. Thus, treatment of severe functional mitral regurgitation with percutaneous techniques or surgery in the early period may be considered to protect right ventricular function in the long term.

Ethics Committee Approval: The study protocol was approved by the Health Science Univercity, Kartal Koşuyolu High Specialization Training and Research Hospital Ethics Committee (date: 25.09.2018; no: 2018.6/15-114). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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