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ORIGINAL ARTICLE

Functional mitral regurgitation and left ventricular systolic dysfunction in the recent era of cardiovascular clinical practice, an observational cohort study

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Functional mitral regurgitation (MR) is frequently associated with left ventricular systolic dysfunction (LVSD). Ventricular volume overload that occurs in patients with MR may lead to a progression of myocardial dysfunction. However, the prevalence and clinical outcomes of functional MR in Japanese patients with LVSD remain unclear. The aim of the present study is to clarify the prevalence and prognosis of functional MR in Japanese LVSD patients in the contemporary era. We followed patients with LVSD (LV ejection fraction (LVEF) $\leqslant$40%) who were listed within a single, hospital-based cohort in the Shinken Database from 2004 to 2011, which was composed of all new patients ($n=17\,517$) who visited the Cardiovascular Institute. A total of 506 patients were included: 86 FMR (moderate-to-severe functional MR) patients and 420 non-FMR (none or mild functional MR) patients. FMR patients were older, had lower rates of hypertension and ischemic heart disease but had higher rates of chronic kidney disease, dilated cardiomyopathy and New York Heart Association III/IV classification. FMR patients had higher brain natriuretic peptide levels and lower LVEF. The Kaplan–Meier curves revealed that the incidence of all-cause death, cardiovascular death and heart failure (HF) admission was significantly higher in FMR patients. The presence of FMR was independently associated with a significantly higher risk of composite end point, including all-cause death and/or HF admission (hazard ratio 1.551, 95% confidence interval 1.045–2.303, $P=0.029$). FMR was common in Japanese patients with LVSD and was associated with adverse long-term outcomes. Future study is warranted to establish the optimal therapeutic strategy for FMR and LVSD.
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Keywords: functional mitral regurgitation; left ventricular dysfunction; prognosis

INTRODUCTION

Patients with left ventricular (LV) dysfunction often have mitral regurgitation (MR). The mechanism of MR includes apical and posterior displacement of the papillary muscles, which results in abnormal coaptation of the mitral leaflets. Annular dilation may also contribute to the creation of MR.[1] This condition is termed as functional MR and is frequently observed in patients with LV systolic dysfunction (LVSD).[2,3] Chronic MR leads to further depression in LV contractility[4] and may result in adverse outcomes through a progressive spiral of LV remodeling.[5]

Previous studies conducted in Western countries have shown that the presence of MR in patients with LVSD was associated with poor prognosis.[3,5,6] In contrast, the epidemiology of cardiovascular disease in Japan is different from that of Western countries with respect to ethnic background and etiology. Moreover, previous reports regarding functional MR and LVSD were based on clinical practices in the 1980s to 1990s.[7,8] Sophisticated patient care and cutting edge therapeutic strategies have prolonged the lifespan of patients with heart failure (HF), and the management of severe HF patients, such as with advanced LV remodeling, has become more important recently. Therefore, functional MR has attracted more attention in the contemporary era of HF management. However, little is known about the current prevalence and prognosis of functional MR in Japanese patients with LVSD in real-world clinical settings. Thus we examined a hospital-based cohort from the Shinken Database using data obtained between 2004 and 2011.[9–11] In the present study, we aimed to clarify the current prevalence and long-term clinical outcomes of FMR in Japanese LVSD patients by using a hospital-based cohort.

METHODS

Study population and protocol

The Shinken Database is composed of all new patients at the Cardiovascular Institute in Tokyo, Japan ('Shinken' is an abbreviated name in Japanese for the name of the hospital), excluding patients with active cancer and any foreign travelers.[9–11] The principal aim of this hospital-based database is to survey the

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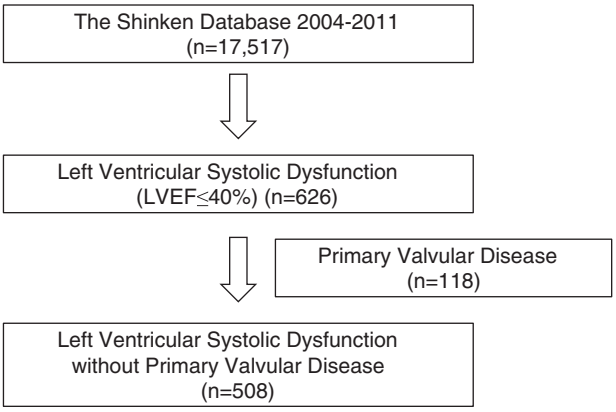

Figure 1 Patient flow chart. From the 2004–2011 Shinken Database, which included 17 517 new visiting patients, 626 patients were found to have LVSD (LV ejection fraction ⩽40%). Among these, we excluded patients with primary valvular heart disease ($n=118$). Finally, 508 patients were examined in this study.

prevalence and prognosis of cardiovascular diseases in urban areas of Japan.[12] The registry started in June 2004, and thereafter, patients have been continually registered to the database annually. The data in the present study were derived from this database between June 2004 and March 2012 (Shinken Database 2004–2011), including 17 517 new visiting patients. Of these patients, 626 patients were found to have LVSD (LV ejection fraction (LVEF) ⩽40%). We excluded patients with primary valvular heart disease ($n=118$). Valvular heart disease was defined as long-standing mitral or aortic valve involvement, as documented by physical examination, echocardiography and angiography. Finally, 508 patients were examined and tracked for an average of 978 ± 789 days in this study (Figure 1).

Ethics

The ethics committee at the Cardiovascular Institute granted permission for this study, and all of the patients gave written informed consent. The study was performed in accordance with the Declaration of Helsinki.

Data collection

After obtaining the electrocardiogram and chest X-ray readings, cardiovascular status was evaluated in each patient using echocardiography, an exercise test and blood laboratory data according to the attending physician's decision within 3 months after the first visit. All echocardiographic studies were performed as part of routine clinical care. MR, as assessed by color Doppler echocardiography, was performed at the first hospital visit (HP Sonos 5500, Philips Medical Systems, Andover, MA, USA; SSD 6500, Aloka, Mitaka, Tokyo, Japan; iE33, Phillips Medical Systems, Andover, MA, USA; Pro Sound α10, Aloka, Mitaka, Tokyo, Japan; Vivid E9 GE Healthcare Japan, Hino, Tokyo, Japan; Artida, Toshiba Medical Systems, Otawara, Tochigi, Japan). Functional MR was diagnosed based on the findings of normal leaflet structures with a maximum systolic position of one or both mitral leaflets above the mitral annulus level. The severity of the MR (none, mild, moderate and severe) was determined by more than two experienced echocardiographers without the knowledge of the patients' background and was based on the quantitative assessment by visually comparing the turbulent flow jet area with the left atrial area.[13] Patients were divided into two groups according to the baseline MR grade: 86 FMR (moderate-to-severe functional MR) patients and 420 non-FMR (none or mild FMR) patients. The following were collected as the initial clinical parameters: sex, age, drug information, and coexisting conditions. The following echocardiographic parameters were also collected: LV end-diastolic dimension, LV end-systolic dimension, interventricular septum thickness, posterior wall thickness, and LVEF. The estimated glomerular filtration rate was calculated using the glomerular filtration rate equation for the Japanese population: glomerular filtration rate $= 194 \times (\text{serum creatinine})^{1.094} \times (\text{age})^{0.287} \times (0.739 \text{ if female})$.[14] Chronic kidney disease was defined as an estimated glomerular filtration rate $<60\,\text{ml}\,\text{min}^{-1}\,1.73\,\text{m}^{-2}$.[14,15] Idiopathic dilated cardiomyopathy was diagnosed by the presence of global LV dilatation with impaired systolic function occurring in the absence of known cardiac causes. Hypertrophic cardiomyopathy was diagnosed by echocardiography when hypertrophy (interventricular septum thickness or posterior wall thickness >12 mm) without hypertension was present. We confirmed the deaths of study patients from the medical records of our hospital or from the obtained follow-up information. Surgical mitral valve intervention included surgical mitral valve repair or placement.

Patient follow-up

The health status of patients, incidence of cardiovascular events and mortality are maintained in the database through a link to the hospital medical records. Study documents on prognosis were sent once per year to patients who have discontinued hospital visits or have been referred to other hospitals.

In the present data analysis, follow-up data after 1 April 2012 were excluded. Therefore, the end of the follow-up period was defined as one of the following three time points: (1) date of death if before 31 March 2012; (2) final hospital visit or the date of the final response to our study documents of prognosis with the confirmation of being alive before 31 March 2012; or (3) 31 March 2012, date of death, final hospital visit, or if the final response to our study questions on prognosis were later than 1 April 2012.

We confirmed the HF events (HF requiring hospitalization or death due to HF), which were classified according to the International Classification of Diseases (tenth revision, code I50) using the medical records of our hospital or from the information obtained during follow-up. Cardiovascular death included death resulting from acute myocardial infarction, sudden cardiac death, death due to HF, death due to stroke and death due to other cardiovascular causes.[16]

Statistical analysis

The categorical and consecutive data of the patients' background characteristics are presented as number (%) and mean ± s.d., respectively. The χ^2 test was used for group comparisons, and the unpaired *t*-test was used to compare the consecutive variables. Long-term event-free survival was estimated using the Kaplan–Meier curves, and the log-rank test was used to assess the significance of differences between the two groups. Cox regression analyses were performed to identify the effects of FMR on the long-term clinical outcomes. In the adjusted Cox regression model, univariate Cox regression analysis was adjusted for the following covariates (step-wise method): age ⩾65 years, hypertension, chronic kidney disease, brain natriuretic peptide (BNP) $\geqslant 100\,\text{pg}\,\text{ml}^{-1}$, ischemic heart disease (IHD), idiopathic dilated cardiomyopathy, New York Heart Association (NYHA) class ⩾II, and renin–angiotensin system inhibitor (RAS-I), diuretics and digitalis use. As a sub-analysis, we compared the characteristics and long-term outcomes of FMR patients with and without surgical MR intervention. A probability value of <0.05 indicated statistical significance. These analyses were performed using the SPSS version 19.0 software (SPSS, Chicago, IL, USA).

RESULTS

Among the 17 517 patients who visited our hospital, a total of 506 patients with LVSD were enrolled in this study. FMR patients were observed in 86 patients (17.0%), whereas 420 were non-FMR patients. FMR patients had lower rates of hypertension, dyslipidemia and ischemic heart disease and higher rates of idiopathic dilated cardiomyopathy. The average BNP level in FMR patients was higher than those in non-FMR patients. FMR patients had a lower prevalence of NYHA II classification but a higher prevalence of NYHA III and IV than non-FMR patients (Table 1). Echocardiography showed that LV end-diastolic dimension and LV end-systolic dimension were greater in FMR patients than in non-FMR patients. LVEF was lower in FMR patients (Table 2). The use of RAS-Is, diuretics and digitalis was more

Table 1 Characteristics of patients

	Non-FMR (n = *420*)	*FMR* (n = *86*)	P-*value*
Age (years)	60.6 ± 13.5	64.1 ± 12.6	0.025
Male sex	82.4%	75.6%	0.141
Hypertension	56.0%	39.5%	0.005
Dyslipidemia	40.0%	37.2%	0.630
Diabetes mellitus	35.7%	26.7%	0.110
CKD	46.4%	73.2%	<0.001
BNP (pg ml^{-1})	666 ± 762	1096 ± 789	<0.001
Etiology			
IHD	42.6%	23.3%	0.001
DCM	27.1%	50.0%	<0.001
HCM	3.6%	1.2%	0.245
HHD	3.3%	0.0%	0.086
TIC	11.4%	12.8%	0.720
NYHA Class			<0.001
I	44.0%	4.7%	
II	28.8%	22.1%	
III	13.1%	37.2%	
IV	14.0%	36.0%	

Abbreviations: BNP, brain natriuretic peptide; CKD, chronic kidney disease; DCM, idiopathic dilated cardiomyopathy; FMR, functional mitral regurgitation; HCM, hypertrophic cardiomyopathy; HHD, hypertensive heart disease; IHD, ischemic heart disease; NYHA, New York Heart Association; TIC, tachycardia induced cardiomyopathy.
Data are expressed as mean ± s.d. or percentage.

Table 2 Echocardiographic parameters

	Non-FMR (n = *420*)	*FMR* (n = *86*)	P-*value*
IVST (mm)	9.2 ± 2.2	7.9 ± 1.9	<0.001
PWT (mm)	8.7 ± 1.9	7.6 ± 1.7	<0.001
LVDd (mm)	59.7 ± 8.1	68.1 ± 9.3	<0.001
LVDs (mm)	51.6 ± 8.6	60.7 ± 9.7	<0.001
LVEF (%)	28.7 ± 8.5	23.2 ± 8.6	<0.001

Abbreviations: FMR, functional mitral regurgitation; IVST, interventricular septum thickness; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; PWT, posterior wall thickness.
Data are expressed as mean ± s.d.

common in FMR patients *vs.* non-FMR patients. Beta-blocker use was comparable between the two groups (Table 3).

Overall, all-cause death (cardiovascular death) occurred in 11.0% (5.5%) of non-FMR patients, compared with 23.3% (17.4%) in FMR patients. HF admission occurred in 37.2% of FMR patients and in 16.9% of non-FMR patients (Table 4).

Kaplan–Meier curves revealed that the rates of all-cause death, cardiovascular death and HF admission were significantly higher in FMR patients *vs.* non-FMR patients (Figure 2). Similarly, the Cox regression analysis with unadjusted models showed that FMR was associated with a significantly higher risk for all-cause death (hazard ratio (HR) 2.076, 95% confidence interval (95% CI) 1.228–3.511, $P = 0.006$), cardiovascular death (HR 3.123, 95% CI 1.629–5.988, $P = 0.001$) and HF admission (HR 2.533, 95% CI 1.688–3.847, $P < 0.001$). The adjusted Cox regression analysis showed that in addition to chronic kidney disease, BNP $\geqslant 100$ pg ml^{-1} and ischemic heart disease, the presence of FMR was still associated with a significantly higher risk for composite end point, including all-cause death and/or HF admission (HR 1.551, 95% CI 1.045–2.303, $P = 0.029$) (Table 5).

Table 3 Medications

	Non-FMR (n = *420*) (%)	*FMR* (n = *86*) (%)	P-*value*
Beta-blockers	51.4	58.1	0.256
Calcium channel blockers	14.0	11.6	0.551
RAS-Is	65.2	77.9	0.022
Statins	29.8	29.1	0.898
Diuretics	60.7	94.2	<0.001
Digitalis	15.0	34.9	<0.001
Nitrate	27.9	33.7	0.274

Abbreviations: FMR, functional mitral regurgitation; RAS-I, rennin–angiotensin system inhibitor.
Data are expressed as percentage.

Table 4 Clinical outcomes

	Non-FMR (n = *420*) (%)	*FMR* (n = *86*) (%)	P-*value*
All-cause death	11.0	23.3	0.002
Cardiovascular death	5.5	17.4	<0.001
HF admission	16.9	37.2	0.001
All-cause death and/or HF admission	25.7	51.2	<0.001

Abbreviations: FMR, functional mitral regurgitation; HF, heart failure.

In a sub-analysis, we compared the background characteristics of FMR patients between patients with and without surgical MR intervention. Among FMR patients ($n = 86$), 36 (42%) had undergone surgical MR intervention. Patients who had undergone surgery tended to be younger than those who had not undergone surgery. The prevalence of hypertension was lower in patients who had undergone surgical MR intervention than in those who had not undergone surgical MR intervention. The average BNP level and NYHA class was comparable between the two groups. The etiology of LVSD was not different between the two groups (Supplementary Table S1). Echocardiography showed that LV wall thickness was thinner and LV dimension was greater in patients who had undergone surgical MR intervention than in those who had not undergone surgical MR intervention (Supplementary Table S2). Calcium channel blockers tended to be commonly used in patients who had undergone MR surgery than in those who had not undergone surgical MR intervention (Supplementary Table S3). The Kaplan–Meier curve showed FMR patient mortality for patient who had and had not undergone surgical MR intervention (Log-rank $P = 0.190$; Figure 3). Similar to the Kaplan–Meier curve in Figure 3, the univariate Cox regression analysis showed that surgical MR intervention was not associated with long-term mortality (HR 1.790, 95% CI 0.740–4.329, $P = 0.197$). We adjusted the univariate Cox regression analysis with the following covariates: age $\geqslant 65$ years, hypertension, LV end-diastolic dimension, and calcium channel blocker use. After these adjustments, surgical MR intervention was not associated with long-term mortality (HR 2.188, 95% CI 0.781–6.128, $P = 0.136$).

DISCUSSION

The present study was performed in an observational cohort of patients with LVSD, and the results of this study demonstrated the prevalence and clinical outcomes of Japanese FMR patients in a recent, real-world, clinical setting. The major findings of the present study were as follows: (1) FMR was complicated in 17.0% of LVSD

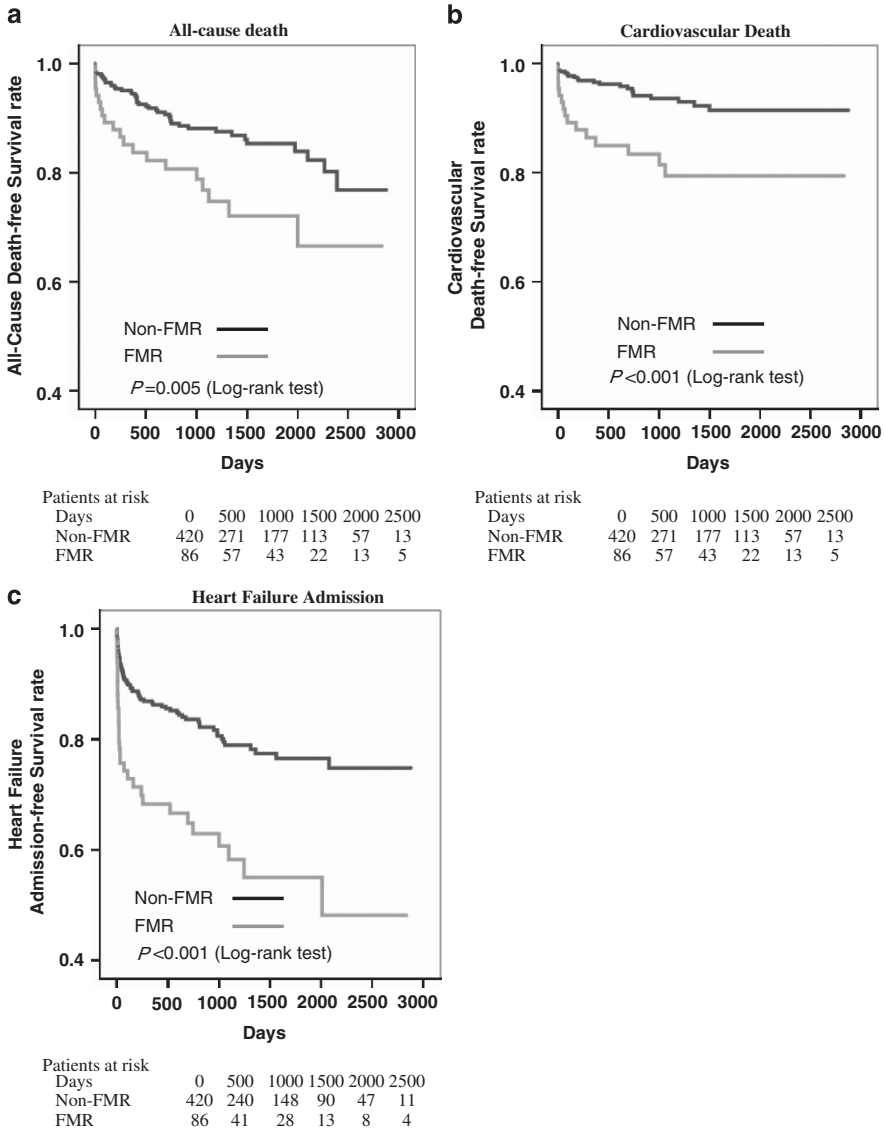

Figure 2 Kaplan–Meier curves for (**a**) all-cause death-free survival rate, (**b**) cardiovascular death-free survival rate and (**c**) heart failure admission-free survival rate. Kaplan–Meier curves revealed the rates of all-cause death (**a**), cardiovascular death (**b**) and HF admission (**c**) were significantly higher in FMR patients than in non-FMR patients.

Table 5 HR for all-cause death and/or heart failure admission

	P-*value*	*HR*	*95% CI*
Functional MR	0.029	1.551	1.045–2.303
CKD	<0.001	2.148	1.464–3.152
BNP $\geqslant 100\,pg\,ml^{-1}$	0.008	2.849	1.312–6.185
IHD	0.027	1.499	1.047–2.145

Abbreviations: BNP, brain natriuretic peptide; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; IHD, ischemic heart disease; MR, mitral regurgitation.

patients who visited a cardiovascular hospital in Japan, (2) FMR patients had worse background clinical characteristics, such as lower LVEF, higher BNP and higher rates of NYHA III/VI, and (3) the presence of FMR was still associated with higher incidences of all-cause death, cardiovascular death and HF admission in recent, real-world clinical practice in Japan.

Functional MR is a common condition in patients with LVSD, and its prevalence varies according to the severity of HF and the background characteristics of the study patients. Regarding the etiology of LVSD, the prevalence of IHD is different between the Japanese population and patients previously studied in Western countries. Trichon *et al.*[8] reported that the prevalence of IHD in patients with functional MR and LVSD was approximately 60%, whereas this was only 39% in the present study. As previous studies have revealed, the presence of IHD was strongly associated with worse clinical outcomes in HF patients. Furthermore, in the present study, the presence of IHD is associated with higher incidences of all-cause death and/or HF admission. Therefore, the different prevalence of IHD might affect the differences in clinical outcomes between the Western and Japanese populations. Furthermore, previous studies focusing on functional MR and LVSD were based on clinical practices in the 1980s to 1990s.[7,8] Our hospital database started in 2004, and the treatment strategy for LVSD gradually changed from the 1980s to 2000s. In addition, we should pay attention to the ethnic differences

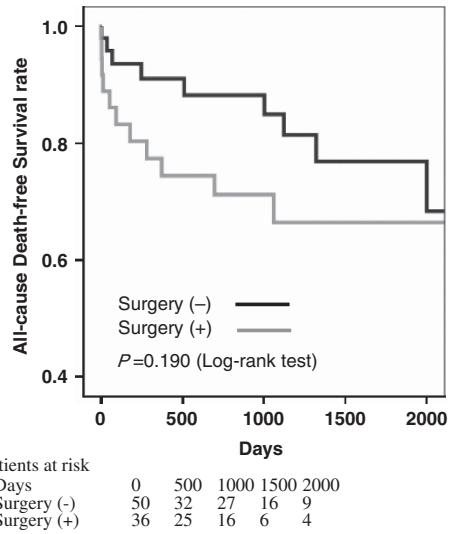

Figure 3 Kaplan–Meier curves for all-cause, death-free survival rate. Kaplan–Meier curve showed that the mortality of FMR patients was comparable between patients who had and had not undergone surgical MR intervention.

in cardiovascular disease. However, to our knowledge, there is limited data focusing on the presentation and long-term clinical outcomes of patients with functional MR and LVSD in clinical practices in Japan.

In the present study, FMR was observed in 17.0% of Japanese patients with LVSD. Along with the previous studies performed in Western countries,[7] FMR patients had worse background clinical characteristics, such as higher BNP levels and more severe HF symptom, compared with those of non-FMR patients (Table 1). The presence of FMR was associated with higher incidences of all-cause death, cardiovascular death and HF admission. Even after covariate adjustments, the presence of FMR was still associated with worse long-term outcomes in patients with LVSD.

The optimal medical treatment for patients with FMR and LVSD is not established. Some anti-hypertensive and cardio-protective drugs, such as beta-blockers and RAS-Is, might have potential. Varadarajan *et al.*[17] reported that the use of beta-blockers was associated with improved survival in patients with severe MR. However, this study included patients with normal LV function. The beneficial effects of beta-blockers for patients with FMR and LVSD need to be clarified. However, RAS-Is also have potential. The administration of ramipril was reported to reduce MR severity in patients with baseline systolic blood pressure $\geqslant$140 mm Hg but not in patients with systolic blood pressure $<$140 mm Hg.[18] Beta-blockers and RAS-Is are not only anti-hypertensive drugs but also cardio-protective drugs, and these drugs are strongly recommended for patients with LVSD. The clinical impact of beta-blockers and RAS-Is on FMR patients with LVSD through various pharmacological effects, such as blood pressure lowering and protection against further LV remodeling, needs to be clarified. In the present study, the prevalence of hypertension was lower in patients with FMR than those without, and beta-blockers and RAS-Is were administered in 58.1% and 77.9% of patients with FMR and LVSD, respectively. However, we might need to use these potential medications more aggressively to aim for an optimal blood pressure control and cardiac protection for these patients.

Patients with functional MR and advanced HF pose a particularly difficult management dilemma, because the surgical risk of this population is extremely high and the benefits of surgical MR reduction have been variable, inconsistent and suboptimal.[19,20] Along with the previous studies, we could not find any significant differences between patients with and without surgical MR intervention. As shown in the sub-analysis, the background characteristics of study patients were different between the two groups. However, even after adjustments with covariates, there were no significant differences in the long-term survival between these two groups. Early intervention for patients with FMR and LVSD with MR surgery might be a potential option. The optimal surgical candidate and timing of functional MR is still currently unclear. Cardiac resynchronization therapy also has a potential for the treatment of FMR patients.[21] Focusing on the functional MR patients with high operative risk, the therapeutic potential of cardiac resynchronization therapy for moderate to severe functional MR was examined. MR reduction was observed in all patients who survived over 6 months after cardiac resynchronization therapy, and patients with improved MR had better outcomes than those with non-improvers.[22] Percutaneous edge-to-edge mitral valve repair has emerged as a novel therapeutic option for the treatment among them, of severe MR.[23–26] Auricchio *et al.*[27] examined 51 severely symptomatic (NYHA $\geqslant$III) cardiac resynchronization therapy nonresponders with significant FMR underwent percutaneous edge-to-edge mitral valve repair and reported that treatment with percutaneous edge-to-edge mitral valve repair was feasible, safe and demonstrated improved HF symptom, increased LVEF and induced reverse LV remodeling in approximately 70% of the study population. In cases of surgical MR intervention, we should pay attention to aggravated LV function after surgery. Therefore, if we can expect reverse LV remodeling (improved LV function) by percutaneous procedure, percutaneous intervention for FMR might be an attractive option for patients with functional MR and LVSD.

The present study has several clinical implications. Functional MR was frequently associated with advanced LVSD. Therefore, the poor prognosis of patients with functional MR might reflect the adverse outcomes of severe LVSD. However, the presence of functional MR further worsens LV remodeling. Moreover, the recent studies suggested that treating functional MR with percutaneous mitral valve repair improved LV function and resulted in reverse remodeling.[27,28] Thus, paradoxically, it is possible that functional MR has the potential to be a treatable target of advanced LV remodeling.

We recognize several limitations in this study. The sample size of the present study was limited, thus the statistical power might not be sufficient for any negative data to be conclusive. The etiology of LVSD was not determined in 10% of the study populations and may affect the results. We used a semi-quantitative grading of MR in this study. Although the regurgitant jet of functional MR is usually central and correlated well with the regurgitant volume,[29] the quantitative grading of MR might be performed in a further study. Moreover, because of the nature of a single hospital-based cohort, we could not conclude the effect of surgical MR intervention on functional MR and LVSD with only this study. Further studies, especially randomized studies, are needed to clarify the optimal candidate for MR surgery in patients with functional MR and LVSD in the future.

In conclusion, this observational study of a cohort of unselected, Japanese, LVSD patients revealed that FMR was a common condition in LVSD patients. FMR is still currently associated with long-term mortality and HF admission in the cardiovascular clinical practice. Further study is warranted to establish optimal therapeutic strategies for FMR and LVSD.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on Hypertension Research website (http://www.nature.com/hr)