Short-term Clinical Outcomes of Transcatheter Edge-to-edge Repair using MitraClip for Mitral Regurgitation : Experience from a Single Center

Hidetomo Nomi, Yasushi Ueki, Masatoshi Minamisawa, Daisuke Sunohara
Yukari Okuma, Yusuke Kanzaki, Tamon Kato, Soichiro Ebisawa
Hirohiko Motoki, Tatsuya Saigusa* and Koichiro Kuwahara

Department of Cardiovascular Medicine, Shinshu University School of Medicine

Background : As the first commercially available device to treat mitral regurgitation (MR) percutaneously, the MitraClip transcatheter edge-to-edge repair (TEER) system was approved for use in Japan in 2017.

Objective : We evaluated the efficacy and safety of MitraClip TEER during its first year of implementation at our hospital in comparison with previous studies.

Methods : This retrospective study included 23 consecutive patients who underwent MitraClip TEER for MR between October 2021 and September 2022 at Shinshu University Hospital. The primary outcome was MR reduction ≤ 2+ and New York Heart Association (NYHA) class improvement at 30 days.

Results : The majority of the 23 patients (91.2 %) were NYHA class III or IV at baseline. A reduction in MR grade to less than moderate was achieved in all patients at discharge and in 22 (95.7 %) patients at 30 days. NYHA class improvement was observed in 21 (91.2 %) patients at the study end point. No procedural complications were encountered.

Conclusion : The MitraClip TEER procedure improved MR grade and symptoms without any major complications in patients with moderate-to-severe or severe MR. These results corroborated those of earlier reports and demonstrated the short-term efficacy and safety outcomes of the MitraClip at our institution. *Shinshu Med J 72 : 49—59, 2024*

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Key words : mitral regurgitation, heart failure, structural heart disease

I Introduction

The global demographic shift towards an older population has resulted in a higher number of patients with heart failure (HF). Affecting up to 20 % of HF patients, mitral regurgitation (MR) is the most prevalent valvular heart disease and is strongly associated with poor outcomes[1]. While degenerative MR (DMR) is caused by organic disease of the mitral valve leaflet, functional MR (FMR) is related to leaflet tethering with left ventricular or annular dilatation in the absence of leaflet organic disease. The treatment strategy for MR depends on its etiology ; current international guidelines recommend mitral valve surgery for DMR and optimal medical therapy for FMR[2]. In daily practice, however, many patients with DMR do not undergo surgery due to high surgical risk, and FMR patients often remain symptomatic even after optimal medical treatment. The benefit of surgical mitral valve repair on cardiovascular outcomes has also not yet been demonstrated for FMR. Against this background, there has been a clinical need for less invasive treatment for MR.

* Corresponding author : Tatsuya Saigusa
Department of Cardiovascular Medicine,
Shinshu University School of Medicine
3-1-1 Asahi, Matsumoto, Nagano 390-8621, Japan
E-mail : tatsuwan@shinshu-u.ac.jp

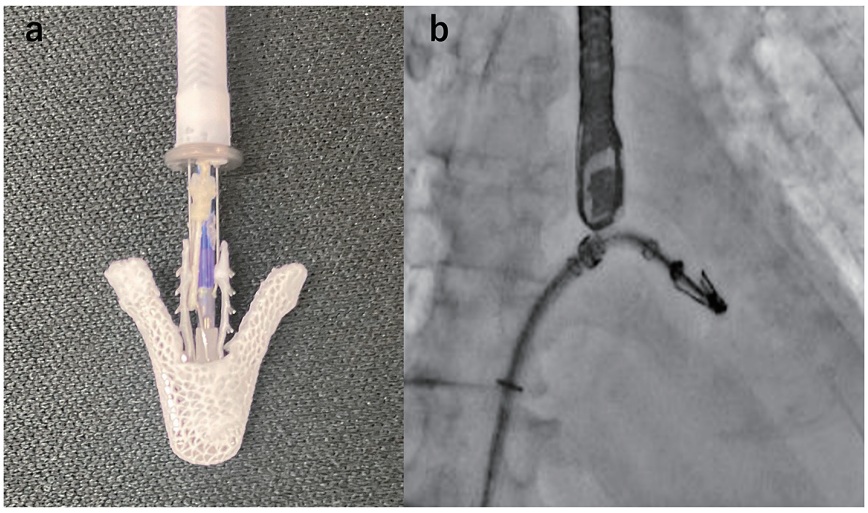

Fig. 1　The MitraClip system
(a) The the MitraClip system. The two arms and grippers grasps the leaflets of the mitral valve. (b) Fluoroscopic image of the MitraClip during procedure.

As the first commercially available device to treat MR percutaneously, the MitraClip TEER system was approved for use in Japan in 2017. The MitraClip grasps and reapproximates mitral valve leaflets to reduce MR. This procedure was first introduced at our institution in October 2021. The present study analyzed the short-term efficacy and safety of the MitraClip TEER procedure in patients with MR during its first year at our hospital.

Ⅱ　Methods

A　Patient population

Twenty-three consecutive patients with moderate-to-severe or severe MR who underwent MitraClip TEER between October 2021 and September 2022 at Shinshu University Hospital were analyzed in this retrospective study. All subjects were determined as appropriate candidates for the MitraClip procedure by a multidisciplinary heart team in accordance with Japanese Circulation Society guidelines[3]. The indications for surgery were moderate-to-severe or severe FMR follwing optimal medical therapy as well as severe DMR patients with high surgical risk.

B　Procedure

The MitraClip (Abbot Vascular, Santa Clara, CA, USA) was used for the study cohort under general anesthesia with fluoroscopic and echocardiographic guidance. **(Fig. 1)** The inter-atrial septum was crossed using standard techniques through a femoral venous access. The MitraClip Steerable Guide Catheter was advanced across the transseptal puncture, and the MitraClip Delivery Catheter was advanced into the left atrium. Then, the MitraClip device was advanced across the mitral valve into the left ventricle and was pulled back to grasp the leaflets. Transesophageal echocardiography (TEE) and color flow doppler were employed to assess the position of MitraClip device and any residual MR. If the MitraClip device was not positioned properly or MR burden was not adequately reduced, repositioning and additional grasping were attempted. When placement was deemed acceptable, the MitraClip device was closed and deployed from the Delivery Catheter. A second MitraClip device was added in cases of significant residual MR if there was adequate mitral valve orifice area to accommodate the second clip without causing mitral valve stenosis. Device time was defined as time between the insertion and removal of the Guide Catheter.

C　Echocardiographic analysis

All patients undergoing the MitraClip procedure were considered suitable for TEER on the basis of pre-procedural transthoracic echocardiography (TTE) and TEE to determine the precise mechanism and severity of MR. TTE was also performed at discharge

and 30 days after procedure. All echocardiograms were obtained by certified echocardiographers and reviewed by several cardiologists to determine the initial severity and etiology of MR, the etiology of post-procedural residual MR, and the status of single leaflet device attachment (SLDA). MR severity was determined according to quantitative criteria adapted from the American Society of Echocardiography and Mitral Valve Academic Research Consortium guidelines[4)5)]. MR was categorized as 0 (none), 1+ (mild), 2+ (moderate), 3+ (moderate to severe), or 4+ (severe). Left ventricular quantitative volume measurements and ejection fraction were obtained by the disk method, and left atrial volume was calculated by the biplane area-length method. MR type was classified based on the anatomical etiology of the mitral complex. Ventricular FMR (VFMR) was defined as MR due to ventricular leaflet tethering with left ventricular remodeling. Atrial FMR (AFMR) was defined as MR stemming from annular and atrial dilatation, with preserved left ventricular ejection fraction. DMR was judged as MR due to prolapse or degeneration of the leaflet. Acute procedural success was defined as MR ≤2+ on post-procedural TEE. The baseline severity of tricuspid regurgitation was determined on the basis of quantitative and semi-quantitative criteria adapted from the American Society of Echocardiography[4)].

D Endpoints and follow-up

The primary efficacy endpoint was MR grade reduction to ≤2+ and NYHA class improvement at 30 days. The secondary efficacy endpoints were changes in echocardiographic parameters, including left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (ESV), left atrial diameter, and biomarkers including brain natriuretic protein (BNP) and estimated glomerular filtration rate (eGFR) between baseline and 30 days. Safety outcomes included major bleeding, stroke, vascular complications requiring intervention, device embolization, cardiac tamponade, and conversion to heart surgery.

E Statistical analysis

Categorical variables were presented as absolute values and percentages, which were analyzed using Fisher's exact test. Continuous variables were expressed as the mean ± standard deviation or median and interquartile range, which were compared with the paired *t*-test or Mann Whitney Wilcoxon test, as appropriate. P-values were 2-tailed, with values of <0.05 considered statistically significant in all analyses. All testing was performed using SPSS software version 28.0 (SPSS, Chicago, Illinois).

Ⅲ Results

A Patient characteristics

A total of 23 consecutive patients who underwent MitraClip TEER were analyzed. Their baseline demographics are summarized in **Table 1** and **Table 2**. Median age was 83 years, and mean Society of Thoracic Surgeons (STS) risk score for mitral valve replacement was 10.5 ± 7.5 %. Eighty-seven percent of patients had a history of acute HF admission within the previous 1 year. The majority of patients (91.2 %) were severely symptomatic (NYHA III/IV). Five patients displayed NYHA class IV symptoms on intravenous inotropes. MR etiologies were ventricular in 14 patients (60.9 %), atrial in 4 patients (17.4 %), and degenerative in 5 patients (21.7 %). Approximately 30 % of patients had non-ischemic cardiomyopathy. MR grade 3+ and 4+ were detected in 7 (30.4 %) and 16 (69.6 %) patients, respectively. Mean effective regurgitation orifice area was 0.43 ± 0.17 cm^2. Patients with VFMR displayed a higher surgical mortality risk score, lower left ventricular ejection fraction, and greater end-diastolic volume than did the other groups. Left atrial volume was greater in the AFMR group. Moderate or severe tricuspid regurgitation was more frequent in the AFMR (100 %) and DMR (80 %) groups compared with the VFMR group (28.6 %).

B Procedural characteristics

The procedural characteristics of MitraClip TEER are presented in **Table 3**. Most patients (78.3 %) were treated with a single clip. A wide type clip was used in 15 (53.6 %) patients. Mean procedure time was 152 min, and device time was 82.7 min. We observed no procedural complications.

C Procedural and clinical outcomes

The changes in MR grade and clinical outcomes are summarized in **Fig. 2** and **Table 3**. MR reduction

Table 1 Baseline characteristics

Age (years)	Sex	BSA (m^2)	Type of MR	Etiology of MR	Type of cardiomyopathy	CFS	NYHA class	STS score (%)	LVEF (%)
80	F	1.3	FMR	Ventricular	DCM	4	3	14.2	34
83	M	1.3	FMR	Ventricular	ICM	3	3	8	33
86	M	1.5	FMR	Atrial	Unclassified	3	3	15.1	63
91	M	1.3	DMR	P3 prolapse	Unclassified	3	3	10.5	62
77	M	1.8	FMR	Ventricular	ICM	3	2	7.9	42
87	F	1.2	FMR	Ventricular	DCM	5	4	8.7	28
53	M	1.5	FMR	Ventricular	DCM	3	4	2.9	26
85	M	1.1	FMR	Ventricular	DCM	5	4	9.2	32
81	M	1.4	FMR	Ventricular	ICM	5	3	33.2	34
89	M	1.6	DMR	A3 prolapse	Unclassified	3	3	12.3	46
57	M	2	FMR	Ventricular	ICM	2	3	29.3	33
83	F	1.4	FMR	Atrial	ICM	3	3	4.8	87
88	F	1.4	FMR	Atrial	Sarcoidosis	4	3	9.1	50
83	M	1.5	DMR	A2 prolapse	Unclassified	3	3	13.2	47
86	F	1.4	FMR	Ventricular	CTRCD	5	4	11.1	26
68	M	1.9	FMR	Ventricular	ICM	2	3	9	22
81	F	1.5	DMR	P2 prolapse	Unclassified	3	2	4.6	78
83	F	1.3	FMR	Atrial	Unclassified	3	3	4.8	73
74	M	1.7	FMR	Ventricular	Sarcoidosis	3	3	4.2	38
67	M	1.5	FMR	Ventricular	AL-CA	5	4	7.2	35
78	M	1.6	FMR	Ventricular	ATTR-CA	2	3	4.1	35
78	M	1.7	DMR	P2 prolapse	Unclassified	4	3	2.6	60
90	M	1.4	FMR	Ventricular	ICM	3	3	17.1	40

Abbreviations : CA, cardiac amyloidosis ; CFS, clinical frailty scale ; CTRCD, cancer therapy-related cardiac dysfunction ; DMR, degenerative mitral regurgitation ; DCM, dilated cardiomyopathy ; FMR, functional mitral regurgitation ; ICM, ischemic cardiomyopathy ; NYHA, New York Heart Association ; STS, Society of Thoracic Surgeons.

to grade 1+ or 2+ was achieved in all patients during the procedure and at discharge. MR recurrence at 30 days was observed in 1 patient with DMR (P3 prolapse). This patient had grade 2+ MR at discharge, which progressed to grade 3+ at 30 days without evidence of SLDA or leaflet tear. One patient with VFMR had mean trans-mitral pressure gradient >5 mmHg at 30 days. NYHA class improved in all cases except for 1 patient with AL amyloidosis and VFMR, in whom the MitraClip successfully decreased MR grade from 4+ to 2+, although NYHA remained class IV. No changes were noted in the grade of tricuspid regurgitation at 30 days, nor were any cases of death, stroke/transient ischemic attack, myocardial infarction, or reintervention of the mitral valves.

D Echocardiographic parameters and biomarkers

The changes in echocardiographic parameters and biomarkers from baseline to 30 days are presented in **Fig. 3**. LVEDV and ESV did not change remarkably in the VFMR and AFMR group, but were reduced in the DMR group. Left atrial diameter decreased considerably in VFMR and DMR groups. There was no significant improvement in BNP level and eGFR before the procedure and after 30 days.

Ⅳ Discussion

The present study revealed several key findings regarding the MitraClip TEER procedure for severe MR. First, transcatheter mitral valve repair was conducted predominantly for severely symptomatic patients at prohibitive surgical risk in our early experience. Second, the MitraClip TEER procedure could be performed successfully, with acute reduction of MR to grade ≤2+ and improvements in HF symptoms in the vast majority of patients. Third, the procedure was conducted without any safety issues.

Table 2 Baseline characteristics according to MR etiology

Characteristic	Overall (N = 23)	Ventricular FMR (N = 14)	Atrial FMR (N = 4)	DMR (N = 5)
Age (years)	83 (78, 86)	79 (70, 85)	85 (83, 86)	83 (81, 89)
Male (%)	16 (69.6)	11 (78.6)	1 (25.0)	4 (80.0)
Hypertension (%)	12 (52.2)	6 (42.9)	4 (100)	2 (40.0)
Dyslipidemia (%)	10 (43.5)	7 (50.0)	2 (50.0)	1 (20.0)
Diabetes mellitus (%)	6 (42.8)	3 (21.4)	2 (50.0)	1 (20.0)
Previous myocardial infarction (%)	6 (26.1)	5 (35.7)	1 (25.0)	1 (20.0)
Previous PCI (%)	7 (30.4)	7 (50.0)	0 (0.0)	1 (20.0)
Previous CABG (%)	3 (13.0)	1 (7.1)	0 (0.0)	0 (0.0)
Previous stroke or TIA (%)	2 (8.7)	1 (7.1)	1 (25.0)	0 (0.0)
COPD (%)	3 (13.0)	0 (0.0)	1 (25.0)	2 (40.0)
History of atrial fibrillation (%)	14 (60.7)	10 (71.4)	4 (100)	1 (20.0)
Previous CRT (%)	2 (8.7)	1 (7.1)	0 (0.0)	1 (20.0)
HF hospitalization within previous 1 year (%)	20 (87.0)	13 (92.9)	4 (100)	3 (60.0)
NYHA class IV (%)	5 (21.7)	5 (35.7)	0 (0.0)	0 (0.0)
Cause of cardiomyopathy				
Ischemic (%)	7 (30.4)	6 (42.9)	1 (25.0)	0 (0.0)
Non-ischemic (%)	16 (69.6)	8 (57.1)	3 (75.0)	5 (100)
Medication				
Beta-blocker (%)	21 (91.3)	14 (100)	4 (100)	3 (60.0)
ACEI, ARB, or ARNI (%)	17 (73.9)	10 (71.4)	3 (75.0)	4 (80.0)
MRA (%)	15 (65.2)	9 (64.3)	3 (75 %)	3 (60.0)
SGLT2 inhibitor (%)	15 (65.2)	12 (85.7)	1 (25.0)	2 (40.0)
Diuretic (%)	21 (91.3)	12 (85.7)	4 (100)	5 (100)
Intravenous inotrope (%)	5 (21.7)	5 (35.7)	0 (0.0)	0 (0.0)
Anticoagulant (%)	14 (69.5)	10 (71.4)	4 (100)	2 (40)
Antiplatelet (%)	5 (21.7)	5 (35.7)	0 (0)	0 (0)
Hemoglobin (g/dL)	12.0 ± 0. 4	11.9 ± 1.9	12.5 ± 1.9	12.2 ± 2.2
Albumin (g/dL)	3.7 ± 0.1	3.5 ± 0.6	3.7 ± 0.5	4.0 ± 0.2
eGFR (mL/min/m^2)	33 (22, 55)	27.5 (22, 43)	51.5 (27.8, 61)	33 (27.5, 64)
BNP (pg/mL)	443 (129, 766)	472 (358, 836)	538 ± 337	132 (88, 754)
STS risk score (%)	10.5 ± 7.5	11.7 ± 8.9	8.5 ± 4.9	8.4 ± 4.5
Echocardiographic assessment				
Severity of MR				
3 +	7 (30.4)	7 (50.0)	0 (0.0)	0 (0.0)
4 +	16 (69.6)	7 (50.0)	4 (100)	5 (100)
Effective regurgitation orifice area (cm^2)	0.43 ± 0.17	0.42 ± 0.19	0.38 ± 0.04	0.50 ± 0.13
Left ventricular end-diastolic dimension (mm)	52.5 ± 11.4	55.0 ± 13.2	48.2 ± 11.1	48.6 ± 3.3
Left ventricular end-systolic dimension (mm)	42.1 ± 14.1	49.1 ± 12.2	29.1 ± 10.7	32.3 ± 5.9
Left ventricular end-diastolic volume (mL)	140.4 ± 73.6	155.3 ± 88.0	109.3 ± 55.5	123.6 ± 13.7
Left ventricular end-diastolic volume index (mL/m^2)	94.4 ± 43.7	104.0 ± 57.5	75.0 ± 34.2	83.1 ± 14.9
Left ventricular end-systolic volume (mL)	83.8 ± 67.2	109.8 ± 74.1	34.8 ± 26.8	50.1 ± 16.3
Left ventricular end-systolic volume index (mL/m^2)	56.0 ± 43.7	73.4 ± 47.7	23.7 ± 17.4	33.2 ± 10.1
Left ventricular ejection fraction (%)	44.5 ± 17.9	32.7 ± 5.6	68.3 ± 15.7	58.6 ± 13.1
Left atrial dimension (mm)	49.9 ± 11.0	47.9 ± 5.6	61.9 ± 20.5	45.9 ± 8.1
Left atrial volume index (mL/m^2)	85.1 ± 56.2	73.5 ± 22.9	144.7 ± 119.5	69.9 ± 25.2
Moderate or severe tricuspid regurgitation (%)	12 (52.1)	4 (28.6)	4 (100.0)	4 (80.0)

Values are presented as the mean ± standard deviation, median (interquartile range), or n (%).
Abbreviations : ACEI, angiotensin converting enzyme inhibitor ; ARB, angiotensin receptor blocker ; ARNI, angiotensin receptor-neprilysin inhibitor ; BNP, brain natriuretic peptide ; CABG, coronary artery bypass grafting ; COPD, chronic obstructive pulmonary disease ; CRT, cardiac resynchronization therapy ; DMR, degenerative mitral regurgitation ; eGFR, estimated glomerular filtration rate ; FMR, functional mitral regurgitation ; PCI, percutaneous coronary intervention ; MRA, mineralocorticoid receptor antagonist ; SGLT2, sodium-glucose cotransporter 2 ; STS, Society of Thoracic Surgeons ; TIA, transient ischemic attack ; HF, heart failure.

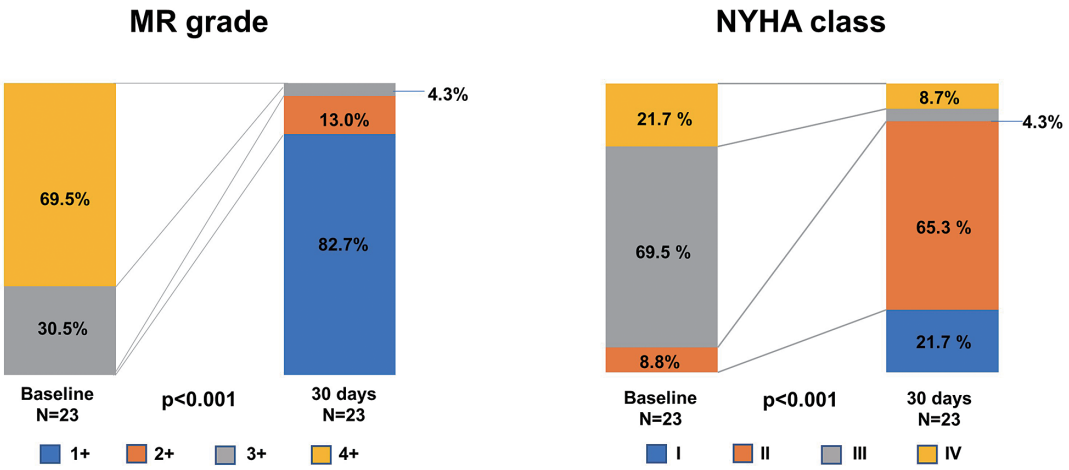

Fig. 2 Changes in MR grade and NYHA class from baseline to 30 days after MitraClip transcatheter edge-to-edge repair
Abbreviations : MR, mitral regurgitation ; NYHA, New York Heart Association.

MR is strongly associated with a poor prognosis and increased risk of HF and mortality. Given the limited therapeutic options in patients at high surgical risk, transcatheter mitral valve repair represents an important advancement for this patient subset not only to reduce MR burden and HF symptoms, but also to improve mortality and HF admission rates, as supported by the growing body of evidence regarding the MitraClip. Our short-term clinical outcomes were comparable to global landmark studies including the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT)[6], and possibly even better considering the more symptomatic patients in our cohort, indicating a successful introduction of the MitraClip TEER procedure at our institution. In our study, approximately 20 % of patients had NYHA class IV symptoms on intravenous inotropes and most suffered from impaired renal function, which limited medical treatment options. In such circumstances, the MitraClip was effective for any type of MR in terms of reducing regurgitation and HF symptoms. Moreover, the procedural outcome was excellent and without major complications. These results were comparable or even superior to those of other trials despite our older and more symptomatic population.

The management of VFMR in particular has long been a clinical challenge since mitral valve surgery has not shown survival benefits. Two randomized controlled trials (RCTs) assessing the efficacy and safety of the MitraClip, Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation (MITRA-FR)[7] and COAPT[6], were published in 2018. Although they targeted the same patient population with the same disease using the same device, their findings were not consistent ; while COAPT showed a significant efficacy of the MitraClip procedure, MITRA-FR demonstrated only neutral results. The possible explanations for this discrepancy include the proportion of left ventricular size and MR severity as well as the optimization of medical therapy. COAPT enrolled a subset of patients having more severe MR, less advanced left ventricular disease (dilatation/systolic dysfunction), and more optimized medical therapy as compared with the MITRA-FR patients. Thus, the COAPT-like profile might be suitable to maximize the advantages of the MitraClip, while patients with overly severe left ventricular dilatation/systolic dysfunction may not benefit from the procedure. This assumption appears reasonable since VFMR is, by nature, the consequence of a diseased left ventricle and not mitral valve leaflets.

A comparison of the above RCTs and the Japan post-marketing surveillance (PMS) study[8] regarding

Table 3 Procedural and clinical outcomes.

	Overall (N = 23)	Ventricular FMR (N = 14)	Atrial FMR (N = 4)	DMR (N = 5)
Procedural characteristics				
Acute procedural success	23 (100)	14 (100)	4 (100)	5 (100)
Number of clips per patient				
1	18 (78.3)	12 (85.7)	4 (100)	2 (40.0)
2	5 (21.7)	2 (14.2)	0 (0.0)	3 (60.0)
Distribution of wide and narrow clips				
Wide clip	15 (53.6)	7 (43.7)	3 (75.0)	5 (62.5)
Narrow clip	13 (46.4)	9 (56.3)	1 (25.0)	3 (37.5)
Procedure time (min)	152.4 ± 42	144 ± 40.3	151.5 ± 31.1	176.8 ± 44.4
Total device time (min)	82.7 ± 28.7	76.3 ± 33.0	83.3 ± 24.2	96.2 ± 23.4
Procedural complications				
Single leaflet device attachment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Major bleeding	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stroke	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular complications resulting in surgical intervention	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Device embolization	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac tamponade	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Conversion to heart surgery	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
MR grade				
Post-procedure				
1 +	20 (87.0)	13 (92.8)	3 (75.0)	4 (80.0)
2 +	3 (13.0)	1 (7.1)	1 (25.0)	1 (20.0)
3 +	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4 +	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discharge				
1 +	18 (78.2)	12 (85.7)	3 (75.0)	3 (60.0)
2 +	5 (21.7)	2 (14.2)	1 (25.0)	2 (40.0)
3 +	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4 +	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Day 30				
1 +	19 (82.6)	13 (92.8)	3 (75.0)	3 (60.0)
2 +	3 (13.0)	1 (7.1)	1 (25.0)	1 (20.0)
3 +	1 (4.3)	0 (0.0)	0 (0.0)	1 (20.0)
4 +	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mean trans-mitral gradient (mmHg)				
Post-procedure	2.4 ± 1.0	2.4 ± 1.1	2.8 ± 0.4	2.2 ± 0.8
Discharge	2.5 ± 1.1	2.3 ± 1.3	3.3 ± 0.8	2.6 ± 0.4
Day 30	2.3 ± 0.8	2.2 ± 0. 7	2.9 ± 0.7	2.5 ± 0.9
Mean trans-mitral gradient ＞5 mmHg				
Post-procedure	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)
Clinical outcomes at 30 days				
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
HF admission	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stroke/Transient ischemic attack	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Reintervention of the mitral valve	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
NYHA class at 30 days				
Ⅰ	6 (26.1)	5 (35.7)	0 (0.0)	1 (20.0)
Ⅱ	14 (60.9)	6 (42.8)	4 (100)	4 (80.0)
Ⅲ	1 (4.3)	1 (7.1)	0 (0.0)	0 (0.0)
Ⅳ	2 (8.7)	2 (14.2)	0 (0.0)	0 (0.0)

Values are presented as the mean ± standard deviation or n (%).
Abbreviations : DMR, degenerative mitral regurgitation ; FMR, functional mitral regurgitation. HF, heart failure ; MR, mitral regurgitation ; NYHA, New York Heart Association.

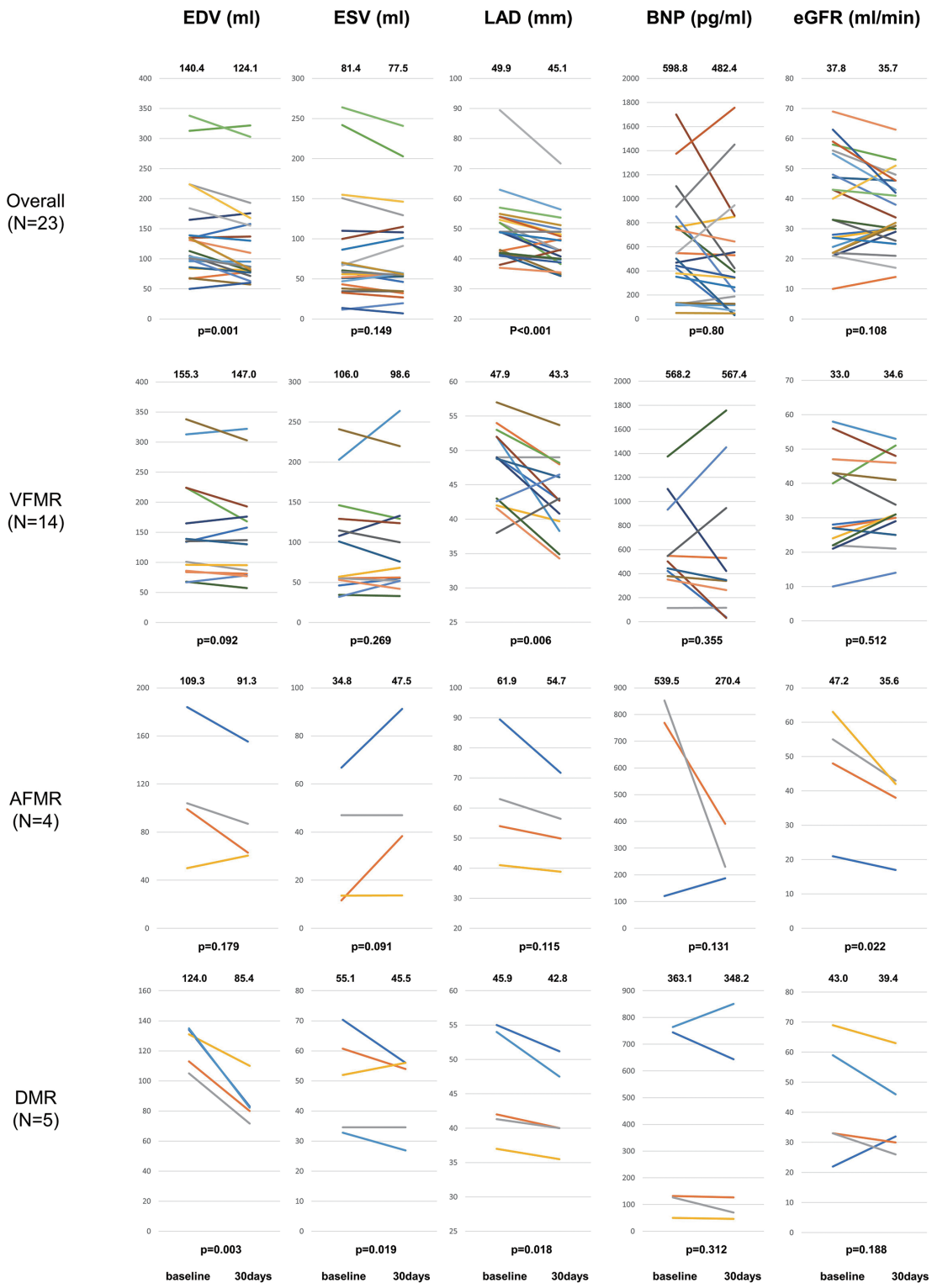

Fig. 3 Changes in echocardiographic parameters and biomarkers from baseline to 30 days after MitraClip transcatheter edge-to-edge repair to MR etiology

Values are presented as the respective means of the baseline and 30 days.

Abbreviations : AFMR, atrial functional mitral regurgitation ; BNP, brain natriuretic peptide ; DMR, degenerative mitral regurgitation ; EDV, end-diastolic volume ; eGFR, estimated glomerular filtration rate ; ESV, end-systolic volume ; VFMR, ventricular functional mitral regurgitation ; LAD, left atrial diameter.

Table 4 Comparisons of key baseline characteristics across studies

	Shinshu University Hospital (N = 14)	COAPT Device Group (N = 302)	MITRA-FR Device Group (N = 152)	Japan PMS FMR group (N = 358)
Age	76.1 ± 11.4	71.8 ± 11.8	70.1 ± 10.1	76.2 ± 9.1
Male (%)	11 (78.6)	201 (66.6)	120 (78.9)	220 (61.5)
Body-mass index (kg/m^2)	20.4 ± 4.5	27.0 ± 5.8	NA	21.1 ± 3.3
History of atrial fibrillation (%)	9 (64.3)	173 (57.3)	49 (35.5)	NA
Previous CRT (%)	1 (7.1)	109 (56.1)	46 (30.5)	81 (22.7)
HF hospitalization within previous 1 year	13 (92.0)	175 (56.1)	NA	40 (11.3)
NYHA class III	4 (28.5)	154 (51.0)	82 (53.9)	173 (50.3)
NYHA class IV	5 (35.7)	18 (6.2)	15 (9.2)	78 (22.7)
Cause of cardiomyopathy				
Ischemic	6 (42.9)	184 (60.9)	95 (62.5)	NA
Non-ischemic	8 (57.1)	118 (39.1)	57 (37.5)	NA
Medication				
Beta-blocker	14 (100)	275 (91.1)	134 (88.2)	265/347 (76.4)
ACEI, ARB, or ARNI	10 (71.4)	216 (71.5)	125 (82.2)	217/347 (62.5)
MRA	9 (64.3)	153 (50.7)	86 (56.6)	153/347 (44.1)
SGLT2 inhibitor	12 (85.7)	NA	NA	NA
Diuretic	12 (85.7)	270/302 (89.4)	151 (99.3)	303/347 (87.3)
Intra-venous inotrope	5 (35.7)	NA	NA	NA
Creatinine clearance (mL/min/m^2)	33.4 ± 14.4	50.9 ± 28.5	NA	NA
STS risk score (%)	11.7 ± 8.9	7.8 ± 5.5	NA	12.4 ± 10.2
Echocardiographic assessment				
Effective regurgitation orifice area (cm^2)	0.42 ± 0.19	0.41 ± 0.15	0.31 ± 0.10	0.36 ± 0.21
Left ventricular end-diastolic dimension (mm)	55.0 ± 13.2	62.0 ± 7.0	NA	NA
Left ventricular end-systolic dimension (mm)	49.1 ± 12.2	53.0 ± 9.0	NA	NA
Left ventricular end-diastolic volume (mL)	155.3 ± 88.0	194 ± 69.2	252 ± 67.0	176.3 ± 79.4
Left ventricular end-diastolic volume index (mL/m^2)	104.0 ± 57.5	101.0 ± 34.0	136.2 ± 37.4	NA
Left ventricular end-systolic volume (mL)	109.8 ± 74.1	135.5 ± 56.1	NA	111.7 ± 66.1
Left ventricular end-systolic volume index (mL/m^2)	73.4 ± 47.7	NA	NA	NA
Left ventricular ejection fraction (%)	32.7 ± 5.6	31.3 ± 9.1	33.3 ± 6.5	39.8 ± 11.5

Values are presented as the mean ± standard deviation or n (%).

Abbreviations : ACEI, angiotensin converting enzyme inhibitor ; ARB, angiotensin receptor blocker ; ARNI, angiotensin receptor-neprilysin inhibitor ; CRT, cardiac resynchronization therapy ; FMR, functional mitral regurgitation ; HF, heart failure ; MRA, mineralocorticoid receptor antagonist ; NA, not available ; SGLT2, sodium-glucose cotransporter 2 ; STS, Society of Thoracic Surgery ; PMS, post-marketing surveillance.

VFMR is summarized in **Table 4**. The subjects in our study were more elderly and had higher STS replacement scores relative to COAPT. Most of the patients had experienced HF admission within 1 year, and one third were NYHA class IV requiring intravenous inotropes before and after the procedure. Such comorbidities as atrial fibrillation and renal failure were more frequent in our population as well. As with the Japan PMS study, the baseline characteristics of our subjects reflected the real-world clinical background of Japanese patients with HF. Guideline-based medical therapy for HF with reduced ejection fraction was even more optimal in our study. The proportion of MR severity (effective regurgitation orifice area) and left ventricular chamber size (LVEDV) in the cohort is presented in **Fig. 4**. Indeed, the subjects displayed a COAPT-like profile with more severe MR and relatively less severe left ventricular remodeling. These factors may have contributed to the efficacy observed in our study.

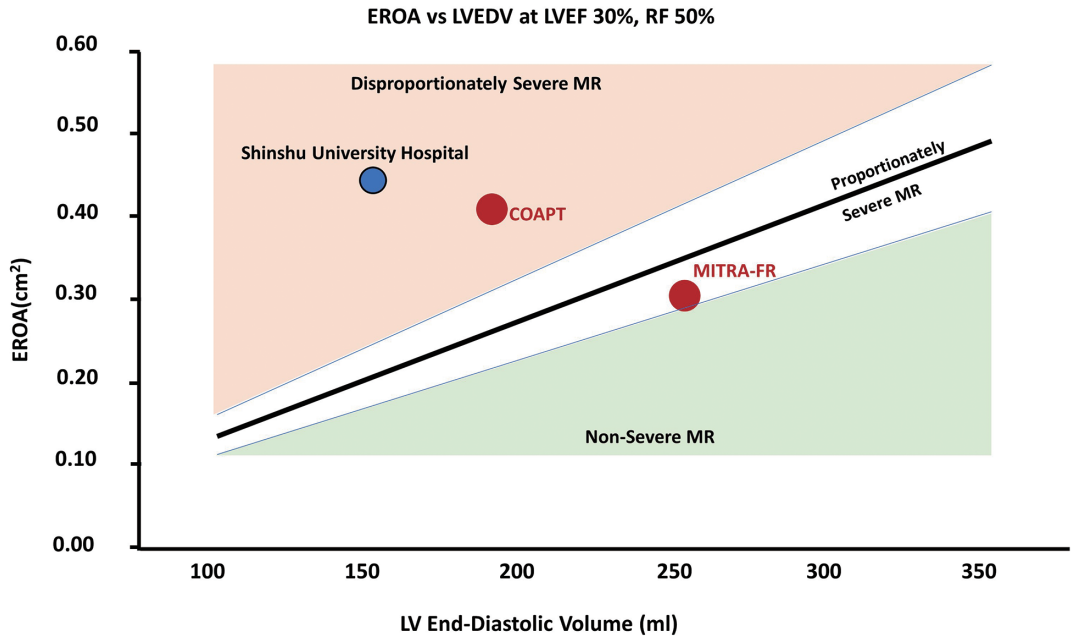

Fig. 4 Relationships between EROA and LVEDV across studies

The black line indicates the hypothetical relationship between EROA and LVEDV when the degree of severe MR is proportional to the LVEDV, assuming a LVEF of 30 % and regurgitant fraction of 50 %. The orange area represents severe MR that is disproportionate to left ventricular dilation. The green area represents non-severe MR. The white area represents a degree of uncertain proportion of MR to LVEDV. The averages of patients enrolled in the MITRA-FR and COAPT trials based on the information made public to date are represented as dots.

Abbreviations : EROA, effective regurgitation orifice area ; LVEDV, left ventricular end-diastolic volume ; LVEF, left ventricular ejection fraction, MR, mitral regurgitation ; RF, regurgitant fraction.

AFMR has been increasingly recognized as an entity without leaflet pathology, for which atrial dilatation and annular remodeling are the main etiologies. Despite the high prevalence and frequent coexistence of atrial fibrillation and MR, little is known on the clinical course and optimal management of AFMR, and current guidelines do not define it as a separate entity. Patients with AFMR tend to be more elderly[9] and are often treated with conservative strategies because of their high surgical risk, especially since medical treatment for HF patients with preserved ejection fraction has limited benefit. Although data on TEER with the MitraClip for AFMR are lacking, favorable results in terms of both symptoms and MR grade were observed in our cohort.

Lastly, TEER using the MitraClip versus surgery for DMR was studied in the EVEREST II trial[10] published in 2011. The RCT showed the superiority of surgery over TEER in terms of long-term MR reduction and freedom from reintervention. However, TEER may be feasible in DMR patients with prohibitive surgical risk and anatomical eligibility. Further contemporary RCTs using the latest MitraClip G4 system for moderate surgical risk are required to assess the efficacy of the MitraClip compared with surgery[11].

A Limitations

Several limitations should be considered in the current study. First, the sample size was small, and data from a single center may lack generalizability. Second, retrospective data collection has the risk of bias, although consecutive patients were analyzed in this study. Third, the control group (e.g. patients not undergoing MitraClip or surgical repair) was not available in the current study, which may result in the inadequate assessment of the efficacy of MitraClip. Fourth, since the follow-up duration was short at 30 days, extended observation is needed to confirm the long-term efficacy and safety of the MitraClip TEER procedure.

V Conclusion

MitraClip TEER resulted in marked improvements in MR grade and symptoms without any procedural complications at 30 days in patients with moderate-to-severe or severe MR. These results support the short-term efficacy and safety of the MitraClip procedure at our institution.

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Conflicts of interest

The authors declare no conflicts of interest regarding this study.

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