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ORIGINAL RESEARCH ARTICLE

Outcome comparison of mitral valve surgery and MitraClip therapy in patients with severely reduced left ventricular dysfunction

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Abstract

Aims The aim of this study was to compare the outcomes of surgical mitral valve repair or replacement (sMVR) and percutaneous edge-to-edge repair using MitraClip (pMVR) in patients with severe left ventricular dysfunction affected by functional mitral regurgitation (FMR).

Methods and results We retrospectively identified 132 patients with left ventricular ejection fraction (LVEF) ≦ 30% submitted to sMVR (n = 47) or pMVR (n = 85) for FMR at our centre from January 2013 to December 2017. To adjust for baseline imbalances, we used a propensity score matching by age, logistic EuroSCORE, and left ventricular end-systolic volume. After being matched, MitraClip therapy showed lower perioperative mortality and rate of complications yet increased residual mitral regurgitation (MR) grade than did surgery (0.2 ± 0.50 in sMVR vs. 1.3 ± 0.88 in pMVR, $P < 0.0001$). According to stratified multivariate Cox model analysis, residual MR severity was an independent risk factor for cardiac death [hazard ratio (HR), 2.81; 95% confidence interval [CI], 1.44–5.48, P = 0.0025] and re-hospitalization for heart failure (HR, 3.07; 95% CI, 1.50–6.29, P = 0.0022) at 1 year follow-up. Stratified multivariable Cox regression analysis at 3 years identified pMVR as risk factor for cardiac death (HR, 0.19; 95% CI, 0.040–0.86, P = 0.031) and re-hospitalization for heart failure (HR, 0.28; 95% CI, 0.077–0.99, P = 0.048).

Conclusions In patients with FMR and LVEF ≤ 30%, MitraClip therapy resulted in lower perioperative complications and mortality than sMVR. However, surgically treated patients who survived the perioperative stage had less residual MR and experienced lower rates of re-hospitalization for heart failure at 1 year and lower cardiac mortality at 1 and 3 years of follow-up than did patients undergoing pMVR.

Keywords Heart failure; Left ventricular dysfunction; Functional mitral regurgitation; MitraClip; Mitral valve surgery

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Introduction

Functional mitral regurgitation (FMR) is frequently observed in patients with ischaemic and non-ischaemic cardiomyopathy and is associated with poor clinical outcome in patients with heart failure (HF) with reduced ejection fraction (HFrEF) due to dilative left ventricular remodelling.[1,2] While FMR is regarded by many as a marker rather than a driver of poor outcome in these patients, non-pharmacological treatment of FMR is frequently considered by the treating physicians of these patients.[3] Although surgical mitral valve repair or replacement (sMVR) is regarded as the gold standard for

therapy, in clinical practice, about 50% of patients with severe FMR are not referred for surgery owing to perceived high surgical risk.[4–6] Frequently, these are elderly patients (age > 80 years) with relevant co-morbidities and severely reduced left ventricular ejection function (LVEF < 30%).[7,8] Since 2013, percutaneous edge-to-edge transcatheter mitral valve repair (pMVR) with the MitraClip system (Abbott Vascular, Menlo Park, CA) for FMR in patients with high risk of perioperative mortality and co-morbidities is available and has become increasingly favoured over sMVR, representing a less invasive beating-heart interventional technique.[9–13] In addition, while the MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) study did not find a significant benefit of sMVR over optical medical therapy, another recent randomized trial ['Cardiovascular outcomes assessment of the MitraClip percutaneous therapy for heart failure patients with functional mitral regurgitation' (COAPT) trial] suggested that pMVR is superior to medical therapy with regard to survival and recurrent hospitalization for HF.[14] In the eyes of many readers, these results further support the use of pMVR with MitraClip in this population, despite the fact that both American and European guidelines only see a low level of evidence (class IIb) to support any procedure for correcting mitral regurgitation in patients with functional, not primary mitral regurgitation.[15,16]

FMR in patients with HFrEF is often associated with functional tricuspid regurgitation, atrial fibrillation, or ischaemic disease. In sMVR, concomitant procedures can be performed to address these conditions including tricuspid valve surgery, maze procedures, and coronary artery bypass grafting (CABG). Meanwhile, pMVR—as a concept of minimal invasive therapy—consists of an isolated intervention on the mitral valve regardless of concomitant abnormalities. In the absence of conclusive evidence from randomized controlled trials, these two strategies have naturally been the subject of a contentious debate to determine which modality is superior in symptomatic patients with HFrEF and FMR.[17] In our study, we sought to compare the clinical outcomes (freedom from re-hospitalization and cardiac death) after sMVR vs. pMVR in symptomatic patients with FMR and severe left ventricular dysfunction (LVEF ≦ 30%).

Methods

Study design and follow-up

This single-centre study was approved by the Institutional Review Board of Sana Heart Center in Cottbus (Germany). Hospital records were screened to retrospectively identify patients with moderate to severe FMR and severely reduced LVEF (≤30%) who were treated in our hospital between January 2013 and December 2017 with pMVR or sMVR. Treatment was performed electively (with elective admission) or urgently (during a non-elective admission for HF). Patients with acute emergency treatment, endocarditis, mitral valve stenosis, sMVR after MitraClip implantation, or redo-sMVR were excluded. The clinical course of all patients was retrospectively reviewed based on patients' charts as assessed in clinical routine preoperatively, post-operatively in the intensive care unit, and at discharge. Follow-up data of clinical status and transthoracic echocardiography were obtained from the patients' general practitioners or private cardiologists by telephone and fax communication and were complete in 91% of patients. The clinical follow-up was closed on 31 December 2018, when the last enrolled patient had completed 1 year of follow-up. Endpoints of the study were first re-hospitalization for HF or cardiovascular death. Re-hospitalization for HF was defined as new-onset or worsening signs and symptoms of HF that require urgent therapy and result in hospitalization.

Surgical procedures

All procedures were performed by experienced board-certified cardiovascular surgeons via median sternotomy or right thoracotomy. sMVR with concomitant procedures including aortic valve replacement, tricuspid valve repair (TVR), CABG, pulmonary vein ablation and other procedures [atrial septal defect (ASD) closure and resection of left atrial appendage] were performed by full sternotomy, if possible. With sternotomy, cardiopulmonary bypass (CPB) was established through direct cannulation of ascending aorta and right atrium vein, or superior vena cava/inferior vena cava in cases requiring TVR and ASD closure. In the right-thoracotomy approach, skin incision in the fourth intercostal space was performed after establishing CPB through femoral artery and vein cannulation. Access to mitral valve was gained either via a direct left atrial or transseptal incision depending on the need for TVR and ASD closure. Standard MV replacement and MV annuloplasty with semi-rigid Colvin–Galloway ring were performed on the arrested heart under normal temperature (36°C). Intraoperative transesophageal echocardiography (TEE) was performed to verify that there was no mitral regurgitation (MR) in MV replacement and residual MR grade 0–1 in MV repair. All patients were treated with warfarin as anticoagulation therapy for three post-operative months.

Interventional procedures

All interventional procedures with MitraClips were by one experienced interventional cardiologist. All clips (arm length 9 mm) were implanted according to standard practices under

general anaesthesia with TEE and fluoroscopic guidance. Maximum residual MR grade 2 at a mean blood pressure of $\geq$ 60 mmHg was regarded as an acceptable procedural result; additional clips were placed until this requirement was met.

Choice of treatment strategy in clinical routine

Patients were regarded as potential candidates for pMVR if they met basic criteria for intervention from the German Cardiac Society.[18] The local heart team (consisting of a cardiologist, a cardiac surgeon, a perfusionist, and a cardio-anaesthetist) discussed the individual therapeutic approach based on age, surgical risk as estimated by logistic EuroSCORE, cardiac and extra-cardiac co-morbidities, and mitral valve morphology as assessed by TEE.

Statistical analysis

Results are expressed as mean ± standard deviation (SD) or as median + 25th to 75th percentile interquartile range for continuous variables, and frequency and percentage for categorical variables. Univariable comparisons were performed with Student's unpaired *t*-test for continuous normally distributed data. The Mann–Whitney *U* test was used for comparisons of non-parametric continuous data and Fisher's exact test for categorical data. Survival and freedom from cardiac events were derived using the Kaplan–Meier method; comparisons were made using the log-rank test. Patient characteristics of the pMVR and sMVR groups were compared, and propensity score (PS) analysis was performed to adjust for the three major aspects where significant differences were detected. Patients undergoing MitraClip therapy were matched on a one-on-one basis to patients undergoing surgical treatment on the basis of PSs by use of nearest-neighbour matching without replacement with a matching tolerance (calliper) of 0.25 and an absolute standardized difference of $\leqq$10%. Rates of freedom from re-hospitalization for HF and cardiac death in the matched cohort were generated using the Kaplan–Meier method, and comparisons were made using the stratified log-rank test. To estimate the independent effects for re-hospitalization for HF and cardiac death, multivariable Cox proportional-hazards regression analysis, also stratified on the matched pairs, was subsequently applied to the matched population to identify any independent predictor of mortality. Covariates were included via stepwise regression analysis using a probability for stepwise entry of 0.05. Candidate covariates were chosen based on previous medical knowledge. *P*-value $<$ 0.05 was considered statistically significant, and all reported *P*-values are two-sided. Statistical analysis was performed using SPSS for windows version 22.0 (IBM Japan, Tokyo, Japan).

Results

Baseline characteristics and perioperative outcomes in the full cohort

A total of 132 patients with moderate to severe FMR and preoperative LVEF $\leqq$ 30% were retrospectively identified and included in the study. Of 132 patients, 47 patients (36%) underwent sMVR (*n* = 28/47, 60% ischemic; *n* = 19/47, 40% non-ischemic) and 85 patients (64%) underwent pMVR (*n* = 41/85, 48% ischemic; *n* = 44/85, 52% non-ischaemic) in our centre. All patients underwent coronary angiography prior to MVR to assess coronary artery state. Demographic and clinical features are shown in *Table 1*.

Patients in the pMVR group were older (*P* = 0.043) and had a higher predicted surgical risk by logistic EuroSCORE (*P* = 0.038) than are sMVR patients. The prevalence of implanted cardioverter defibrillator (ICD) or cardiac resynchronization therapy device therapy, previous cardiac surgery, percutaneous coronary artery intervention, and use of spironolactone were significantly higher in the pMVR than in the sMVR group (*Table 1*). Preoperative echocardiography revealed lower LVEF ($P < 0.001$) and higher LV volumes [$P < 0.001$ for LV end-diastolic volume and $P < 0.001$ for left ventricular end-systolic volume LV end-systolic volume (LVESV)] and reduced right ventricular function (*P* = 0.012 for tricuspid annular plane systolic excursion) in the pMVR group. *Table 2* shows preoperative echocardiography data of both groups in more detail.

In the sMVR group (35% urgent), post-operative MR grade was $\leqq$2 in all patients. In the pMVR group (1.1% urgent), 85 patients had an average of 2.1 ± 0.75 clips with post-interventional MR grade $\leqq$ 2 in 97.6%. Post-operative MR grade at discharge was reduced to a mean ± SD of 0.17 ± 0.44 in sMVR as compared with 1.4 ± 0.69 in pMVR ($P < 0.001$). Intensive care unit (ICU) stay and hospital stay were shorter in the pMVR group ($P < 0.001$); 47% (*n* = 22/47) of sMVR patients were discharged to home as compared with 86% (73/85) in pMVR ($P < 0.001$). There was a trend towards higher in-hospital mortality (*P* = 0.0966) and 30 day mortality (*P* = 0.132) in sMVR that did not reach statistical significance.

Propensity score matching

To minimize potential effects of selection bias and to decrease variability of both groups, a second series of analyses were performed on selected pMVR and sMVR patients with corresponding clinical and echocardiography characteristics on the basis of PS matching.

Table 1 Baseline characteristics of the full cohort and PS-matched cohort; *n* (%) if not otherwise specified

Full cohort	Total *n* = 132	sMVR *n* = 47	pMVR *n* = 85	*P*-value
Age, mean ± SD (years)	70 ± 9.0	68 ± 9.6	72 ± 8.5	0.0429
Age ≧ 80 years old	17 (13%)	3 (6%)	14 (16%)	0.112
Male gender	91 (69%)	28 (60%)	63 (74%)	0.116
Body mass index, mean ± SD (kg/m^2)	26 ± 4.9	27 ± 5.5	26 ± 4.6	0.655
COLD	22 (17%)	7 (15%)	15 (18%)	0.809
Arterial hypertension	118 (89%)	41 (87%)	77 (91%)	0.566
Chronic renal disease	48 (36%)	12 (26%)	36 (42%)	0.0611
Diabetes mellitus	51 (39%)	14 (30%)	37 (44%)	0.138
Logistic EuroSCORE, mean ± SD	31 ± 21	25.0 ± 22	33.5 ± 20	0.0377
EuroSCORE, mean ± SD	16 ± 13	15 ± 13	16 ± 14	0.853
Ischaemic cardiomyopathy	69 (52%)	28 (60%)	41(48%)	0.275
Dilated cardiomyopathy	63 (48%)	19 (40%)	44 (52%)	0.275
Atrial fibrillation	77 (58%)	26 (55%)	51 (60%)	0.713
Previous CRT	43 (33%)	6 (13%)	37 (44%)	<0.001
Previous ICD	46 (35%)	3 (6%)	43 (51%)	<0.001
Previous cardiac surgery	31 (23%)	5 (11%)	26 (31%)	0.0102
Previous percutaneous coronary intervention	45 (34%)	9 (19%)	36 (42%)	0.0121
NYHA functional class, mean ± SD	3.2 ± 0.46	3.2 ± 0.46	3.2 ± 0.46	0.683
NYHA II	2 (2%)	1 (2%)	1 (1%)	
NYHA III	97 (73%)	35 (74%)	62 (73%)	
NYHA IV	33 (25%)	11 (23%)	22 (26%)	
Medication				
ACE inhibitor/ARB	94 (71%)	31 (66%)	63 (74%)	0.856
Beta-blocker	113 (86%)	40 (85%)	73 (86%)	1
Mineralocorticoid receptor antagonist	81 (61%)	17 (36%)	64 (75%)	<0.01
Loop diuretics	118 (89%)	37 (79%)	81(95%)	0.00592
Digitoxin	27 (20%)	6 (13%)	21(25%)	0.119
PS-matched cohort	**Total *n* = 60**	**SMVR *n* = 30**	**PMVR *n* = 30**	***P*-value**
Age, mean ± SD (years)	71 ± 8.3	71 ± 8.5	71 ± 8.2	0.963
Age ≧ 80 years old	6 (10%)	3 (10%)	3 (10%)	1
Male gender	38 (63%)	17(61%)	21(70%)	0.422
Body mass index, mean ± SD (kg/m^2)	27 ± 4.4	26 ± 3.7	28 ± 4.9	0.122
COLD	10 (17%)	5 (17%)	5 (17%)	1
Arterial hypertension	56 (93%)	27 (90%)	29 (97%)	0.612
Chronic renal disease	23 (38%)	9 (30%)	14 (47%)	0.288
Diabetes mellitus	22 (37%)	7 (23%)	15 (50%)	0.06
Logistic EuroSCORE, mean ± SD	30 ± 20	30 ± 24	29 ± 16	0.859
EuroSCORE, mean ± SD	14 ± 13	17 ± 15	11 ± 9.8	0.104
Ischaemic cardiomyopathy	31 (52%)	16 (53%)	15 (50%)	1
Dilated cardiomyopathy	29 (48%)	14 (47%)	15 (50%)	1
Atrial fibrillation	33 (55%)	20 (67%)	13 (43%)	0.119
Previous CRT	16 (27%)	6 (20%)	10 (33%)	0.382
Previous ICD	17 (28%)	1 (3.3%)	16 (53%)	<0.001
Previous cardiac surgery	9 (15%)	4 (13%)	5 (17%)	1
Previous percutaneous coronary intervention	16 (27%)	6 (20%)	10 (3.3%)	0.0292
NYHA functional class, mean ± SD	3.2 ± 0.46	3.2 ± 0.48	3.1 ± 0.43	0.577
NYHA II	2 (3%)	1 (3.3%)	1 (3.3%)	
NYHA III	46 (77%)	22 (73%)	24 (80%)	
NYHA IV	12 (20%)	7 (23%)	5 (17%)	
Medication				
ACE inhibitor/ARB	47 (78%)	19 (63%)	28 (93%)	0.0102
Beta-blocker	53 (88%)	26 (87%)	27 (90%)	1
Mineralocorticoid receptor antagonist	30 (50%)	10 (33%)	20 (66%)	0.0194
Loop diuretics	51 (85%)	24 (80%)	27 (90%)	0.472
Digitoxin	10 (17%)	5 (17%)	5 (17%)	1

ARB, angiotensin receptor blocker; COLD, chronic obstructive lung disease; CRT, cardiac resynchronization therapy; ICD, implanted cardioverter defibrillator.

Table 2 Baseline results of transthoracic echocardiography in the full cohort and the PS-matched cohort; *n* (%) if not otherwise specified

Full cohort	sMVR *n* = 47	pMVR *n* = 85	*P*-value
LVEF mean ± SD (%)	26 ± 5.2	22 ± 5.3	<0.001
MR grade, mean ± SD	3 ± 0.44	3 ± 0.35	0.76
MR grade 2	5 (11%)	5 (6%)	
MR grade 3	38 (81%)	75 (88%)	
MR grade 4	4 (8%)	5 (6%)	
TR grade, mean ± SD	1.6 ± 0.93	1.7 ± 0.75	0.478
TR grade 0	5 (11%)	3 (3.5%)	
TR grade 1	20 (42%)	34 (40%)	
TR grade 2	13 (28%)	37 (43.5%)	
TR grade 3	9 (19%)	11 (13%)	
RVESP, mean ± SD (mmHg)	49 ± 3.1	54 ± 15	0.0731
LVDd, mean ± SD (mm)	70 ± 7.3	73 ± 6.4	0.0674
LVDs, mean ± SD (mm)	63 ± 8.4	66 ± 7.2	0.0974
RVDd, mean ± SD (mm)	40 ± 6.0	39 ± 6.3	0.876
RVDs, mean ± SD (mm)	32 ± 5.7	34 ± 6.2	0.275
LA, mean ± SD (mm)	53 ± 6.5	53 ± 8.4	0.797
TAPSE, mean ± SD (mm)	17 ± 4.2	14 ± 4.6	0.00206
LVEDV, mean ± SD (mL)	197 ± 71	243 ± 68	0.00056
LVESV, mean ± SD (mL)	133 ± 58	182 ± 64	0.00004
LVSV, mean ± SD (mL)	64 ± 30	61 ± 28	0.604
PS-matched cohort	**sMVR *n* = 30**	**pMVR *n* = 30**	***P*-value**
LVEF mean ± SD (%)	25 ± 5.8	22 ± 5.2	0.05
MR grade, mean ± SD	3.0 ± 0.32	3.0 ± 0.32	1
MR grade 2	1 (3.3%)	1 (3.3%)	
MR grade 3	27 (90%)	27 (90%)	
MR grade 4	2 (6.7%)	2 (6.7%)	
TR grade, mean ± SD	1.6 ± 1.0	1.5 ± 0.73	0.549
TR grade 0	3 (10%)	2 (6.7%)	
TR grade 1	13 (43%)	14 (47%)	
TR grade 2	7 (23%)	12 (40%)	
TR grade 3	7 (23%)	2 (6.7%)	
RVESP, mean ± SD (mmHg)	46 ± 12	48 ± 18	0.389
LVDd, mean ± SD (mm)	72 ± 8.0	71 ± 5.2	0.28
LVDs, mean ± SD (mm)	66 ± 9.0	63 ± 6.0	0.165
RVDd, mean ± SD (mm)	41 ± 6.2	39 ± 7.2	0.196
RVDs, mean ± SD (mm)	34 ± 5.6	33 ± 7.4	0.755
LA, mean ± SD (mm)	53 ± 7.4	50 ± 5.7	0.14
TAPSE, mean ± SD (mm)	16 ± 4.8	14 ± 4.2	0.0503
LVEDV, mean ± SD (mL)	217 ± 71	215 ± 58	0.923
LVESV, mean ± SD (mL)	149 ± 61	151 ± 50	0.882
LVSV, mean ± SD (mL)	68 ± 30	64 ± 27	0.611

EDV, end-diastolic volume; ESV, end-systolic volume; LA, left atrium; LVDd, left ventricular diastolic diameter; LVDs, left ventricular systolic diameter; LVEF, left ventricular ejection fraction; MR, mitral valve regurgitation; RVDd, right ventricular diastolic diameter; RVDs, right ventricular systolic diameter; RVESP, right ventricular end-systolic pressure; SV, systolic volume; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid valve regurgitation.

Baseline characteristics and perioperative outcomes in the propensity score-matched cohort

Based on the results of the logistic regression analysis, significant differences in characteristics of sMVR and pMVR groups were found for age, logistic EuroSCORE, and LVESV.[19] Accordingly, PS matching was performed for age, logistic EuroSCORE, and LVESV (absolute standardized difference 1%, 5%, and 4%, respectively), resulting in 30 matching pairs of pMVR and sMVR subjects. In the PS-matched cohort, only ICD implantation, history of PCI, systolic pulmonary hypertension, and preoperative use of renin–angiotensin–aldosterone system-directed medication remained different (*Table 1*). Results of echocardiography in the matched cohort are shown in *Table 2*. In sMVR, simple MV repair/replacement was performed in eight patients (27%), while 22 patients underwent additional procedures (CABG, *n* = 14; tricuspid valvuloplasty, *n* = 7; ablation, *n* = 5). In pMVR, a mean of 2.1 ± 0.73 clips was used with an acute success rate of 93%. Post-operative MR grade at discharge was reduced to a mean of 0.20 ± 0.50 in sMVR, compared with a mean of 1.33 ± 0.88 in pMVR ($P < 0.0001$, *Table 3*). In the PS-matched cohort, one pMVR patient with ischaemic cardiomyopathy who had entered the MitraClip procedure in prior cardiogenic shock subsequently died of low output syndrome. In contrast, four sMVR patients died post-operatively (cardiogenic shock, *n* = 2; right HF, *n* = 1; septic shock, *n* = 1) at a mean of 6.5 ± 3.3 days despite the use of extracorporeal membrane oxygenation (ECMO) therapy in three (*Table 4*). In pMVR, 25 patients (83%) could be extubated in the hybrid operation hall, and no patients had major perioperative events such as stroke, cardiac tamponade, or clip-related complications. ICU stay and hospital stay were shorter in the pMVR group ($P < 0.001$). The rate of discharge to home was higher in pMVR than in sMVR ($P \leq 0.001$). Differences in in-hospital mortality ($P = 0.36$) or 30 day mortality ($P = 0.67$) between the two groups did not reach statistical significance (Table *S1*).

Comparison of early and midterm outcomes for re-hospitalization and cardiac death

For the full cohort, median follow-up was 24 months for sMVR [inter-quartile range (IQR) 13–42 months, range 0–65 months] and 23 months for pMVR (IQR 8.4–34 months, range 0.17–70 months). In sMVR, there were no cases of endocarditis, early degeneration of the implanted valve prosthesis, or severe valvular dysfunction requiring redo-surgery during the follow-up period. In pMVR, three patients required surgical revision due to recurrent severe MR with partial clip detachment, and four patients needed second-intervention clip implantations for recurrent severe MR. On Kaplan–Meier analysis of the un-matched cohort, the rates of freedom from re-hospitalization for HF and cardiac death were significantly higher for sMVR at 3 years of follow-up ($P = 0.0013$ and $P = 0.0037$, respectively) (Figure *1*).

In the PS-matched cohort, re-hospitalization for HF and cardiac death was not significantly different in sMVR vs. pMVR groups (stratified log-rank test: $P = 0.28$ and $P = 0.15$, respectively) (*Figure 2*). The rates of freedom from re-hospitalization for HF and cardiac death were the same

Table 3 Procedural characteristics of PS-matched cohort; *n* (%) if not otherwise specified

	sMVR	pMVR	
	n = 30	*n* = 30	*P*-value
Urgent	12 (40%)	1 (3%)	0.00105
Elective	18 (60%)	29 (97%)	0.00105
Isolated MV replacement or repair	8 (27%)	—	—
MV replacement + additional procedures	22 (73%)	—	—
MV repair	8 (27%)	—	—
Redo-surgery	4 (13%)	—	—
Sternotomy	24 (80%)	—	—
RT approach	6 (20%)	—	—
ACC, mean ± SD (min)	62 ± 23	—	—
ECC, mean ± SD (min)	107 ± 36	—	—
MitraClip, mean ± SD	—	2.1 ± 0.78	—
Procedural success rate (MR □ 2 grade)	30 (100%)	28 (93%)	0.492
Concomitant procedures			
AVR	4 (13%)	—	—
TVR	7 (23%)	—	—
CABG	13 (43%)	—	—
LA ablation	5 (17%)	—	—
LAA closure	4 (13%)	—	—

ACC, aortic cross clamping; AVR, aortic valve replacement; CABG, cardiopulmonary bypass grafting; ECC, extracorporeal circulation; LAA, left atrial appendage; MV, mitral valve; RT, right thoracotomy; TVR, tricuspid valve repair.

Table 4 Cases of perioperative death in PS-matched cohort (pMVR *n* = 1, sMVR *n* = 4)

Nr.	Age (years)/ gender	DCM/ ICM	LVEF	Technical approach	Mode of death	Survival (days)	log EuroSCORE
pMVR 1	64/male	ICM	10%	1 clip	Low output syndrome, cardiogenic shock	8	43.6
sMVR 1	74/male	ICM	23%	redo-MVR + CABGx3 IABP + ECMO	Low output syndrome, cardiogenic shock	4	37.2
2	78/male	DCM	20%	MVR + TVR	Septic shock	11	43.5
3	66/male	DCM	10%	MVR + TVR + AVR IABP + ECMO	Low output syndrome, cardiogenic shock	4	33.0
4	78/male	ICM	21%	MVR + TVR ECMO	Right heart failure	7	84.5

AVR, aortic valve replacement; CABG, coronary artery bypass grafting; DCM, dilated cardiomyopathy; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pumping; ICM, ischaemic cardiomyopathy; MVR, mitral valve replacement; TVR, tricuspid valve repair.

at 4 months. Within 4 months after pMVR, three patients died of HF, of which one patient was associated with residual MR grade 4 and the other two had MR grade ≤ 2. At 1 year, the rates of freedom from re-hospitalization for HF in sMVR and pMVR were 90% (95% CI, 0.79–1.00) and 73.3% (95% CI, 0.58–0.89%), respectively ($P = 0.19$); and the rates of cardiac death in sMVR and pMVR were 90% (95% CI, 0.79–1.00) and 73.3% (95% CI, 0.58–0.89), respectively ($P = 0.094$). When comparing only the patients who survived the perioperative phase in the matched cohort ($n = 26$ in sMVR vs. $n = 26$ in pMVR), the rates of freedom from re-hospitalization and cardiac death were significantly higher in the sMVR group than in the pMVR group ($P = 0.009$ and $P = 0.009$, respectively) at 1 year follow-up. This advantage of the sMVR group remained statistically significant at 3 years of follow-up for freedom from cardiac death ($P = 0.043$), but not for freedom from re-hospitalization for HF (stratified log-rank test; $P = 0.12$) (*Figure S1*). New York Heart Association grade in survivors at 1 year follow-up was not significantly different with 2.2 ± 0.59 in sMVR vs. 2.2 ± 0.79 in pMVR patients ($P = 0.89$).

At stratified multivariable Cox regression analysis at 1 year follow-up, post-operative MR severity represented an independent risk factor for re-hospitalization [hazard ratio (HR), 3.07; 95% CI, 1.5–6.3, $P = 0.0022$] and cardiac death (HR, 2.8; 95% CI, 1.4–5.5, $P = 0.0025$) across all matched patients (Table *S2*). Stratified multivariable Cox regression analysis at 3 years identified pMVR (vs. sMVR) as risk factor for cardiac death (HR, 0.19; 95% CI, 0.040–0.86, $P = 0.048$) and for re-hospitalization for HF (HR, 0.28; 95% CI, 0.077–0.99, $P = 0.048$). Also, an elevated grade of residual tricuspid valve regurgitation (TR) acted as a risk factor for cardiac death (HR, 2.69; 95% CI, 1.14–0.99, $P = 0.048$) (Table *S3*).

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Figure 1 Clinical outcome of full cohort. Kaplan–Meier curves for freedom from re-hospitalization (A) and freedom from cardiac death (B) for sMVR (red line) vs. pMVR (black line), showing better outcome for sMVR at 3 years (log-rank $P = 0.0013$ and $P = 0.0037$, respectively). sMVR, surgical mitral valve repair or replacement; pMVR, percutaneous edge-to-edge repair using MitraClip.

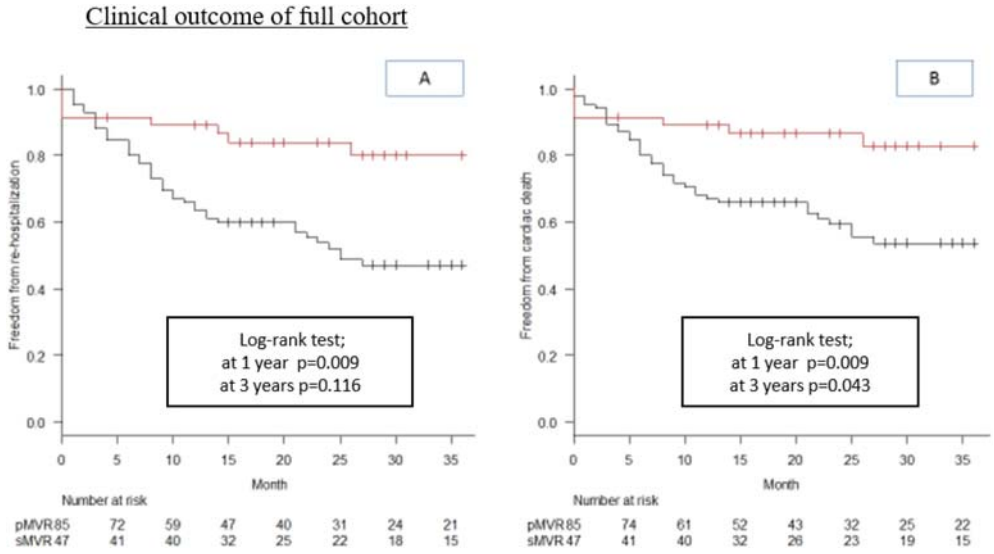
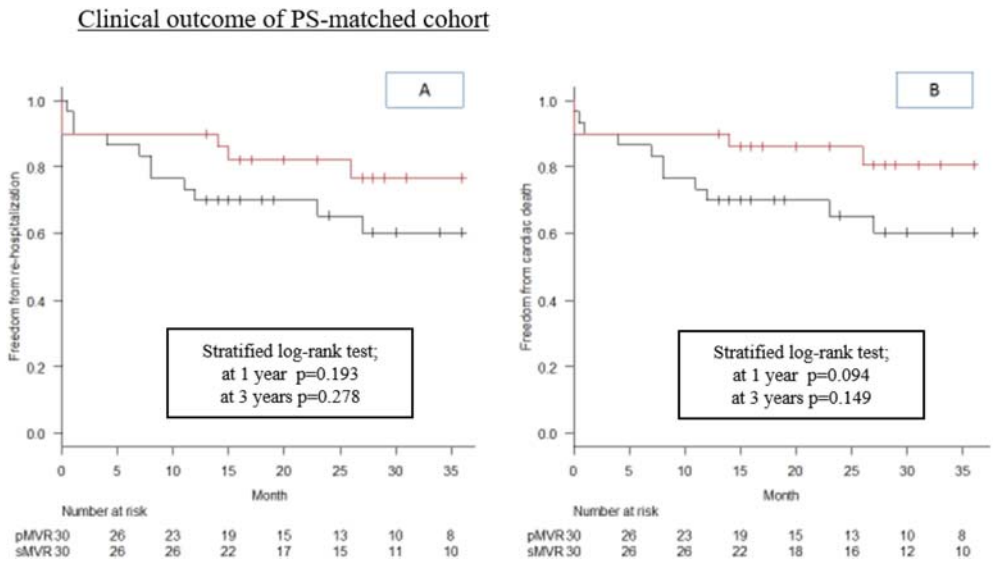


Figure 2 Clinical outcome of PS-matched cohort. Kaplan–Meier curves for freedom from re-hospitalization (A) and freedom from cardiac death (B) for sMVR (red line) vs. pMVR (black line), showing better outcome regarding both events for sMVR at 1 year (stratified log-rank test $P = 0.193$ and $P = 0.094$, respectively) and 3 years (stratified log-rank test $P = 0.278$ and $P = 0.149$, respectively). pMVR, percutaneous edge-to-edge repair using MitraClip; PS, propensity score; sMVR, surgical mitral valve repair or replacement.



Discussion

In this study, we compared the clinical outcomes of two different therapeutic approaches in symptomatic patients with severely reduced ejection fraction and functional MR: sMVR, which allows for full repair/replacement and concomitant surgical procedures yet requires cardiac arrest, and pMVR using edge-to-edge repair, a less comprehensive approach performed on a beating heart.

There are two main findings of the current study. First, in a cohort of HFrEF patients with treated FMR, perioperative mortality is higher in patients with sMVR than pMVR, yet when surviving the perioperative stage, sMVR is significantly associated with longer freedom from re-hospitalization

($P = 0.048$) and cardiac death ($P = 0.030$) during 3 years of follow-up as compared with pMVR. Second, residual MR is associated with cardiac death and re-hospitalization due to HF at 1 year follow-up ($P < 0.01$); in pMVR, residual MR grade was an independent risk factor for re-hospitalization for HF and cardiac death.

Outcome in surgical mitral valve replacement or repair and percutaneous edge-to-edge transcatheter mitral valve repair

As expected, pMVR was found to be safer than surgery regarding peri-procedural risk. With an acute success rate of 97.6% (defined as post-operative MR grade $\leqq 2$), the functional results of pMVR in our cohort were better than those recently reported in the MITRA-FR and COAPT trials.[14,20] Perioperative mortality in the PS-matched pMVR group was only 3.3%, based on one death in a patient presenting with preoperative cardiogenic shock. More than 90% of pMVR patients were stable on medical HF therapy and could be discharged home, even if LVEF was poor. In contrast to sMVR, there were no such complications as respiratory failure with need for re-intubation, bleeding requiring blood transfusion, or stroke. On the other hand, several patients in the sMVR group needed short-term circulatory support including ECMO and intra-aortic balloon pump. Other sMVR patients had to undergo redo-thoracotomy owing to severe perioperative bleeding, which was associated with prolonged post-operative ICU stay. In the PS-matched analysis, perioperative mortality in the sMVR group reached 13% as opposed to 3.3% in the pMVR group, even if the difference was not statistically significant ($P = 0.36$).

The picture changed once the perioperative stage was over. Four months after the procedure, the same number of patients had died from cardiac death in both groups (13%). At 1 year of follow-up, mortality and rate of re-hospitalization for HF were significantly higher in the MitraClip group than in the surgical group, with the difference in mortality remaining significant until 3 years of follow-up despite the relatively low number of cases available for analysis at this time point. Thus, for those patients who survive the perioperative stage, a surgical approach to treating FMR in HFrEF seems to be superior to percutaneous edge-to-edge repair.

Our results indicate that the reason for the favourable midterm/long_x2010;term outcome of short-term sMVR survivors might be related to the more effective reduction in mitral valve regurgitation in sMVR. There were only four sMVR patients with residual MR $>$ grade 0 (vs. 26 pMVR), and none of these four were free from re-hospitalization and cardiac death. In pMVR, residual MR grade was an independent risk factor for cardiac death and re-hospitalization for HF at 1 year follow-up. According to Notomi et al., post-operative LVEF is reduced early (1 to 6 months) after correction for mitral regurgitation in severely reduced LVEF, when the MR volume is fully eliminated or at least significantly reduced.[21] In our study, the severity of residual MR was lower in the sMVR group ($P < 0.001$), and sMVR patients exhibited more reduced post-operative LV function than pMVR patients. Accordingly, more patients in the PS-matched cohort died of cardiogenic shock in the days after sMVR than after pMVR. During 1 year of follow-up, only one patient undergoing pMVR needed mitral valve surgery owing to recurrence of severe MR with mitral ring dilatation, indicating that the durability of the procedural result might be comparable in pMVR and sMVR. However, residual MR (as assessed immediately after the procedure) had a strong impact on cardiac death and re-hospitalization for HF. Owing to the nature of the MitraClip procedure, pMVR rarely achieved full resolution of MR, while sMVR frequently did.[17] Accordingly, the HRs for cardiac death (HR, 0.33; 95% CI, 0.089–1.2, $P = 0.095$) and re-hospitalization for HF (HR, 0.33; 95% CI, 0.090–1.2, $P = 0.10$) at 1 year follow-up were lower after sMVR compared with pMVR. Thus, HFrEF patients with FMR whose left ventricles were able to tolerate the immediate effects of full resolution of MR on the long run seemed to benefit more from sMVR than from pMVR.

Interestingly, residual TR was also an independent risk factor for cardiac death in our study (HR, 2.69; 95% CI, 1.1–6.4, $P = 0.024$), pointing at the important role of the right ventricle in advanced stages of HF. According to previous studies, up to 19% of patients with severe FMR have moderate to severe TR associated with a poor clinical course of HF.[22,23] At the moment, interventional strategies for the treatment of FMR address the mitral valve only, whereas sMVR is frequently combined with TVR when TR is present. While TR is seen by many as a consequence rather than a cause of poor RV function, its correction might still be worthwhile in a situation where an optimization of LV haemodynamics is attempted by MVR. Our results support the hypothesis that combined interventions for MR and TR or early interventions for residual TR should be performed in cases where TR is moderate or severe.[24]

According to a recent article analysing the results of COAPT and MITRA-FR, the degree of LV dilatation may indicate if patients will benefit from pMVR or not.[25] Our Transthoracic echocardiography (TTE) parameters representing LV dilatation (LVEF, LV end-diastolic diameter, and LVESV) in sMVR were comparable with those in MITRA-FR, but survival at 3 years of follow-up in our sMVR patients (81%) was superior to MitraClip patients in both COAPT and MITRA-FR. Our results may support that sMVR is superior to pMVR in patients with HFrEF and dilated left ventricle.[25]

Study limitations

In our study, there are various limitations. This is a non-randomized retrospective, single-centre observational study with

a limited number of patients. Owing to this design, the higher risk patients would be selected naturally for non-open surgery; therefore, the intrinsic risk of patients receiving pMVR would potentially be higher. In addition, differences in frailty could be a factor rejecting patients to open surgery, but it might not be reflected in the PS-matched analysis, which in turn might potentially affect the outcome of patients after pMVR. Moreover, our TTE data were evaluated by experienced cardiologists, but not adjudicated by an external core lab. Thus, conclusions from our study should be taken with caution until confirmed by prospective and randomized clinical trials such as the currently ongoing MATTERHORN trial (NCT 02371512).

Conclusions

In a single-centre retrospective analysis of patients with FMR and severely reduced LVEF, MitraClip therapy resulted in lower perioperative complications and mortality than surgical therapy but yielded less reduction in FMR. In contrast, surgically treated patients who survived the perioperative stage had less residual MR and experienced lower rates of re-hospitalization for HF at 1 year as well as lower cardiac mortality at 1 and 3 years of follow-up than patients undergoing pMVR.

Conflict of interest

None declared.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Outcome of perioperative survivors (excluding cases with peri-operative death) of PS-matched cohort.
Table S1. Perioperative course of PS-matched cohort; n (%) if not otherwise specified. There were no cases of myocardial infarction or AV blockage. ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; AV, atrioventricular; ICU, intensive care unit; LVEF, left ventricular ejection fraction; MR, mitral valve regurgitation; TR, tricuspid valve regurgitation.
Table S2. Cox regression model analysis at 1-year follow-up. DCM, dilated cardiomyopathy.
Table S3. Cox regression model analysis in 3 years follow-up. DCM, dilated cardiomyopathy.

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