Risk Stratification of Percutaneous Edge-to-Edge Repair by MitraClip in Patients with Mitral Regurgitation

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Summary
Edge-to-edge repair using the MitraClip system is indicated in patients with severe mitral regurgitation (MR) who are at high risk for open-heart surgery due to comorbidity or reduced cardiac function. However, less is known about pre-procedural risk factors for mortality and morbidity following MitraClip implantation. Consecutive 25 patients with severe MR who underwent MitraClip therapy (mean age, 77 years old, 14 males) were included. Right heart catheterization and echocardiographic data before and after the procedure were collected and their prognostic impacts were investigated. Acute procedural success was 96%. At one week following MitraClip repair, left ventricular ejection fraction (LVEF) remained unchanged and left ventricular end-diastolic volume tended to be smaller. Cardiac index and mean pulmonary artery pressure (mPAP) were markedly improved following the procedure ($P < 0.001$ for both). In the multivariate analyses using baseline characteristics, both lower LVEF (hazard ratio 0.57, 95% confidence interval 0.30-0.89) and higher mPAP (hazard ratio 1.23, 95% confidence interval 1.06-1.56) were independently associated with post-procedural 1-year death or heart failure readmission ($P < 0.05$ for both). The lower LVEF and higher mPAP group had lower 1-year survival free from HF readmission compared with those without (16.7% versus 100%; $P < 0.001$). In conclusion, a combination of baseline mPAP and LVEF might be a useful tool in predicting post-MitraClip procedural clinical outcomes.

Key words: Heart failure, Hemodynamics, Valve disease

Mitral regurgitation (MR) is the most frequent valvular disease. Historically, approximately half of the patients with severe MR cannot undergo surgical intervention due to their advanced age, renal failure, and/or markedly reduced cardiac function. They receive only guideline-directed medical therapy, including cardiac resynchronized therapy if applicable, but their prognoses have not been satisfactory.

The MitraClip system (Abbott Vascular, Menlo Park, CA, USA), which involves a trans-catheter edge-to-edge repair of the mitral valve, obtained a CE mark for the use of degenerative MR and functional MR in Europe in 2008, was approved for only degenerative MR by the United States Food and Drug Administration in 2013, and was approved for insurance reimbursement in Japan in 2018.

In 2018, the COAPT trial showed a favorable result for survival and freedom from heart failure readmission following the MitraClip procedure. According to the COAPT data, the FDA expanded the indication for the MitraClip to functional MR in 2019. On the contrary, the MITRA-FR trial showed no clinical advantage of the MitraClip treatment over guideline-directed medical therapy alone. Given that these two opposite results might come from different inclusion criteria, appropriate patient selection would be needed for successful MitraClip therapy. In this study, we investigated the pre-procedural factors that are associated with worse clinical outcomes following the MitraClip procedure.

Methods

Patient selection: Data of consecutive patients who received percutaneous edge-to-edge mitral valve repair using the MitraClip system between September 2018 and October 2019 and were followed at our institution for one year were retrospectively collected.

Patients with moderate-severe or greater MR and who were at high risk for a surgical procedure ($n = 25$) were selected for MitraClip treatment. The approach was via a transfemoral vein through the trans-atrial septum following atrial septal puncture using a radiofrequency needle. The mitral valve was clipped by the MitraClip system that was delivered using a 24-Fr steerable guiding catheter and a clip delivery system from the left ventricular side with simultaneous monitoring by trans-esophageal echocardiography.
cardiography during the procedure.

The procedural endpoint was to improve the MR severity to less moderate. One patient was excluded because he had received repeated MitraClip procedures due to a single leaflet device attachment. This study was performed in accordance with the Declaration of Helsinki and the ethical standards of the Committee on Human Experimentation of the University of Toyama. Written informed consent was obtained from all participants beforehand.

Data collection: Preoperative baseline characteristics including demographics, transthoracic echocardiographic findings, and hemodynamic data were collected. Postoperative data were collected one week and 6 months after the MitraClip procedure. Data on all-cause death and heart failure readmission were collected during the one-year observational period following the MitraClip procedure as a primary endpoint.

Statistical analyses: Statistical analyses were performed with JMP Pro 14 (SAS Institute Inc., Cary, NC, USA). Two-sided $P$-values $< 0.05$ were considered statistically significant. Continuous variables are expressed as the median and interquartile or mean and standard deviation. Categorical variables are expressed as numbers and percentages. The paired t-test was performed to compare the coupled data.

Cox proportional hazard ratio regression analyses were performed to identify pre-procedural predictors of death or heart failure readmission during the one-year observational period (i.e., primary endpoint). Variables with $P < 0.05$ in the univariate analyses were included into the multivariate analyses. Receiver operating characteristic (ROC) analyses were performed to calculate cutoffs of parameters for the primary endpoint. Kaplan-Meier analyses and log-rank tests were performed to compare clinical outcomes stratified by the cutoffs.

### Results

#### Baseline characteristics: The baseline characteristics of the 25 study patients are shown in Table I. Median age was 77 (range, 72 to 86) years and the mean STS score was 8.3 ± 5.0%. Most of the patients had functional MR. All patients received guideline-directed medical therapy unless contraindicated. A beta-blocker was prescribed in 86% of the functional MR patients. The doses of anti-heart failure agents were increased as much as possible by cardiologists with expertise in heart failure.

Laboratory, echocardiographic, and hemodynamic data are summarized in Table II. Plasma B-type natriuretic peptide (BNP) level was 388.6 (198.3, 515.0) pg/mL. Left ventricular ejection fraction (LVEF) and end-diastolic volume were 30% and 138 mL, respectively. Mean pulmonary artery pressure (PAP), pulmonary artery wedge pressure (PAWP), and cardiac index were 20 mmHg, 12 mmHg, and 2.1 L/minute/m², respectively.

| Table I. Clinical Characteristics of Patients Who Underwent Edge-to-Edge Repair Using Mitra-Clip |
|---|---|---|
| n | Overall | FMR | DMR |
|---|---|---|---|
| Age, years | 77 [72-86] | 76 [72-82] | 86 [67-91] |
| Male, n (%) | 14 (56) | 12 (57) | 2 (50) |
| Body surface area, m² | 1.52 [1.32-1.62] | 1.52 [1.33-1.61] | 1.42 [1.20-1.67] |
| Systolic BP, mmHg | 93 [88-112] | 94 [88-114] | 91 [88-108] |
| Diastolic BP, mmHg | 54 [50-68] | 60 [50-69] | 54 [49-56] |
| Heart rate, bpm | 74 [67-79] | 74 [68-79] | 70 [55-80] |
| Persistent AF, n (%) | 9 (36) | 7 (33) | 2 (50) |
| Paroxysmal AF, n (%) | 9 (36) | 9 (43) | 0 (0) |
| Diabetes mellitus, n (%) | 4 (16) | 4 (19) | 0 (0) |
| ESRD on HD, n (%) | 2 (8) | 2 (10) | 0 (0) |
| Past history of thoracic surgery, n (%) | 3 (12) | 3 (14) | 0 (0) |
| Post CRT implantation, n (%) | 6 (24) | 6 (29) | 0 (0) |
| STS score, % ± SD | 8.3 ± 5.0 | 9.0 ± 5.1 | 5.0 ± 3.0 |
| Medication | | | |
| β blocker, n (%) | 21 (84) | 18 (86) | 3 (75) |
| RAS inhibitor, n (%) | 21 (84) | 17 (81) | 4 (100) |
| Loop diuretic, n (%) | 19 (76) | 16 (76) | 3 (75) |
| Dose of loop diuretic, mg | 20 [20-40] | 20 [20-40] | 20 [5-35] |
| Torvaptan, n (%) | 17 (68) | 17 (81) | 0 (0) |
| MRA, n (%) | 19 (76) | 17 (81) | 2 (50) |
| SGLT2 inhibitor, n (%) | 4 (16) | 4 (19) | 0 (0) |
| PIMO, n (%) | 9 (36) | 9 (43) | 0 (0) |
| Anticoagulant agent, n (%) | 18 (72) | 16 (76) | 2 (50) |

Data given as mean [25 percentile–75 percentile], mean ± SD or n (%). FMR indicates functional mitral regurgitation; DMR, degenerative mitral regurgitation; BP, blood pressure; AF, atrial fibrillation; ESRD, end stage renal failure; HD, hemodialysis; CRT, cardiac resynchronization therapy; RAS, renin angiotensin aldosterone system; MRA, mineral corticoid receptor antagonist; SGLT2, sodium glucose cotransporter; and PIMO, pimobendan.
Table II. Laboratory Data, TTE Measurements, and Pre-Procedural Hemodynamics of Patients Who Underwent Edge-to-Edge Repair Using MitraClip

|                      | Overall | FMR | DMR |
|----------------------|---------|-----|-----|
| Laboratory data      |         |     |     |
| Serum creatinine, mg/dL | 1.29 [0.99-1.81] | 1.29 [1.10-1.97] | 1.15 [0.91-1.45] |
| Hemoglobin, g/dL      | 10.7 [10.0-12.2] | 10.7 [10.0-12.2] | 10.8 [9.3-12.3] |
| Sodium, mEq/L         | 138 [135-140] | 138 [135-140] | 140 [135-140] |
| BNP, pg/mL            | 388.6 [198.3-515.0] | 437.5 [209.7-576.8] | 215.0 [161.9-266.0] |
| Log BNP               | 2.59 [2.30-2.71] | 2.64 [2.32-2.76] | 2.33 [2.21-2.42] |
| TTE findings          |         |     |     |
| LA volume, mL         | 82.2 [55.5-120.0] | 78.0 [55.5-120.0] | 93.0 [52.8-139.3] |
| LV end-diastolic dimension, mm | 64.0 [56.0-71.0] | 65.0 [59.0-71.0] | 51.5 [44.0-66.5] |
| LVEF (m-Simpson), %   | 30 [25-52] | 28.0 [24.0-38.0] | 55.0 [61.8-61.3] |
| LVEDV, mL             | 138.0 [91.4-186.5] | 145.0 [95.9-186.5] | 87.5 [64.5-172.0] |
| Mitral valve area, cm² | 3.99 [3.54-4.45] | 4.2 [3.5-4.5] | 3.8 [3.3-5.2] |
| Severity of MR, degree ± SD | 3.1 ± 0.7 | 3.0 ± 0.7 | 3.8 ± 0.5 |
| EROA, cm²             | 0.30 [0.23-0.42] | 0.28 [0.23-0.36] | 0.58 [0.48-0.65] |
| Regurgitant volume, mL | 46 [33-62] | 45 [30-56] | 65 [63-69] |
| TAPSE, mm             | 16.5 [12.8-21.0] | 15.2 [12.4-19.6] | 21.7 [20.3-23.3] |
| Hemodynamics          |         |     |     |
| CVP, mmHg             | 5.0 [3.5-8.5] | 5.0 [2.5-9.0] | 5.5 [4.3-7.5] |
| mean PAP, mmHg        | 20.0 [14.5-33.0] | 23.0 [14.5-34.0] | 16.5 [14.3-19.5] |
| PAWP, mmHg            | 12.0 [8.3-24] | 16.5 [8.3-24.0] | 10.5 [8.5-11.0] |
| Cardiac index, L/minute/m² | 2.1 [1.8-2.4] | 2.0 [1.7-2.2] | 3.0 [2.2-3.7] |

Data given as mean [25 percentile–75 percentile], mean ± SD or n (%). FMR indicates functional mitral regurgitation; DMR, degenerative mitral regurgitation; BNP, B type natriuretic peptide; LA, left atrium; LV, left ventricle; EF, ejection fraction; EDV, end-diastolic volume; EROA, effective regurgitant orifice area; TAPSE, tricuspid annular plane systolic excursion; RV%FAC, right ventricle percent fractional area change; CVP, central venous pressure; PAP, pulmonary arterial pressure; and PAWP, pulmonary artery wedge pressure.

Table III. Predictors of Death Or HF Readmission

|                      | Univariate analyses | Multivariate analyses |
|----------------------|----------------------|----------------------|
|                      | HR (95% CI) | P value | HR (95% CI) | P value |
| Demographics         |           |         |           |         |
| Age, per 1 year      | 0.98 (0.90-1.08) | 0.717 |           |         |
| Body surface area, per 0.1 m² | 1.10 (0.70-1.81) | 0.660 |           |         |
| SBP, per 1 mmHg      | 1.01 (0.96-1.06) | 0.629 |           |         |
| Persistent atrial fibrillation | 0.40 (0.02-2.52) | 0.364 |           |         |
| STS score, per 1 point | 1.07 (0.90-1.24) | 0.389 |           |         |
| Echocardiography     |           |         |           |         |
| LA volume, per 1 mL  | 0.98 (0.94-1.0) | 0.090 |           |         |
| LVDd, per 1 cm       | 1.03 (0.96-1.11) | 0.357 |           |         |
| LVEF, per 1%         | 0.87 (0.70-0.98) | 0.010 | 0.57 (0.30-0.89) | 0.001 |
| EROA, per 0.1 cm²    | 0.99 (0.48-1.80) | 0.974 |           |         |
| TAPSE, per 1 mm      | 0.90 (0.73-1.05) | 0.208 |           |         |
| Laboratory data      |           |         |           |         |
| Albumin, per 1 g/dL  | 0.47 (0.06-4.04) | 0.467 |           |         |
| Serum creatinine, per 1 mg/dL | 1.21 (0.65-1.56) | 0.241 |           |         |
| Log BNP, per 1       | 2.24 (0.41-8.61) | 0.312 |           |         |
| Hemoglobin, per 1 g/dL | 1.41 (0.92-2.08) | 0.108 |           |         |
| Hemodynamics         |           |         |           |         |
| CVP, per 1 mmHg      | 1.01 (0.78-1.26) | 0.966 |           |         |
| mean PAP, per 1 mmHg | 1.10 (1.01-1.21) | 0.025 | 1.23 (1.06-1.56) | 0.002 |
| PAWP, per 1 mmHg     | 1.07 (0.97-1.18) | 0.169 |           |         |
| Cardiac index, per 0.1 L/minute/m² | 0.86 (0.71-1.01) | 0.070 |           |         |

Data are presented as HR and 95% CI. HR indicates hazard ratio; SBP, systolic blood pressure; LA, left atrium; LVDd, left ventricle end diastolic dimension; EF, ejection fraction; EROA, effective regurgitant orifice area; TAPSE, tricuspid annular plane systolic excursion; BNP, B type natriuretic peptide; CVP, central venous pressure; PAP, pulmonary arterial pressure; and PAWP, pulmonary artery wedge pressure.
In this study, we investigated the prognostic factor of death or heart failure readmission following the MitraClip procedure, and found that baseline higher PAP (> 21 mmHg) and lower LVEF (< 29%) were associated with death or heart failure re-admission after the procedure.

Controversy concerning efficacy of MitraClip® procedure: Prospective randomized control trials comparing a guideline-directed medical therapy arm versus a MitraClip procedure: During the one-year observational period, 4 patients died and 4 patients had heart failure readmissions. Among the 4 patients with heart failure readmissions, 2 died during the index hospitalization. Single leaflet device attachment occurred in one patient each in functional MR and degenerative MR. All MR were well-controlled within a mild degree. The cause of death was congestive heart failure in two patients, ventricular fibrillation in 1, and pulmonary pneumonia in 1, all of which occurred in the functional MR cohort.

Prognostic impact of baseline characteristics on the post-procedural outcome: Among the baseline variables, lower LVEF and higher mean PAP were significant predictors of the primary endpoint (i.e., death or heart failure readmission). Similarly, in the multivariate analysis, lower LVEF (hazard ratio 0.57, 95% confidence interval 0.29-0.89) and higher mean PAP (hazard ratio 1.23, 95% confidence interval 1.06-1.56) remained independent predictors of the primary endpoint (P < 0.05 for both; Table III). The cutoffs of LVEF and mean PAP to satisfy the primary endpoints calculated using ROC analyses were 29% and 21 mmHg, respectively.

Stratification of clinical outcomes using LVEF and mean PAP: An LVEF of 29% and mean PAP of 21 mmHg stratified the one-year survival free from heart failure readmission into two cohorts (P = 0.008 and 0.061, respectively; Figure 1A, B). It is worth noting that those with both lower LVEF and higher mean PAP (n = 6) had significantly lower survival free from heart failure readmission compared to those without (n = 19, P = 0.0009; Figure 1C). The one-year survival rates free from heart failure readmission for the groups with high EF and low PAP, either low EF or high PAP, and low EF and high PAP were 100%, 91.7%, and 16.7%, respectively.

In 13 patients in whom the 6-month data following the MitraClip procedure are available, LVEF, PAW, plasma B-type natriuretic peptide, and cardiac index remained unchanged during the 6-month observational period among those with baseline lower LVEF and baseline higher mean PAP, as well as among others (P > 0.05 for all). On the contrary, mean PAP and pulmonary vascular resistance (PVR) worsened significantly among those with both baseline lower LVEF and baseline higher mean PAP (P < 0.05 for both; Figure 2).

Discussion

In this study, we investigated the prognostic factor of death or heart failure readmission following the MitraClip procedure, and found that baseline higher PAP (> 21 mmHg) and lower LVEF (< 29%) were associated with death or heart failure re-admission after the procedure.

Controversy concerning efficacy of MitraClip® procedure: Prospective randomized control trials comparing a guideline-directed medical therapy arm versus a MitraClip procedure...

Figure 1. A: Kaplan-Meier curves for death or heart failure readmission-free survival according to high or low ejection fraction before MitraClip procedure. The cut-offs were determined on receiver operating characteristic curves with univariate analysis. B: Kaplan-Meier curves for death or heart failure readmission-free survival according to high or low mean pulmonary arterial pressure before MitraClip procedure. The cut-offs were determined on receiver operating characteristic curves with univariate analysis. C: Kaplan-Meier curves for death or heart failure readmission-free survival according to 3 groups. Red: high EF & low PAP, green; either low EF or high PAP, blue; low EF & high PAP.
Figure 2.  A: Changes in mean pulmonary artery pressure before, after and 6 months after MitraClip for each group with lower EF and higher PAP group and other. B: Changes in pulmonary vascular resistance before, after and 6 months after MitraClip for each group with lower EF and higher PAP group and other.

add-on arm were conducted to investigate the prognostic impact of MitraClip on the functional MR: The MITRA-FR trial\textsuperscript{6} and COAPT trial\textsuperscript{5} have been reported thus far. The MITRA-FR trial showed no significant difference in the composite primary endpoint, i.e., all-cause death and unplanned heart failure rehospitalization. In contrast, in the COAPT trial, the MitraClip add-on arm had a better 24-month heart failure re-admission rate and lower all-cause mortality compared to the medical arm. Inclusion criteria may be one of the causes for such opposite results between these trials.\textsuperscript{7}

The MITRA-FR trial patients had a more enlarged left ventricle (135 ± 35 mL/m\textsuperscript{2} versus 101 ± 34 mL/m\textsuperscript{2}) and reduced left ventricular ejection fraction (15-40% versus 20-50%) compared with the COAPT trial patients. The degree of MR was lower in the MITRA-FR trial than in the COAPT trial (effective regurgitant orifice area, 31 ± 10 mm\textsuperscript{2} versus 41 ± 15 mm\textsuperscript{2}).
Currently, the indication of MitraClip in MR patients is (1) symptomatic MR refractory to guideline-directed medical therapy; (2) high operative risk; (3) severe MR; and (4) anatomical feature applicable to the procedure. However, these inclusion criteria do not consider any other factors such as hemodynamic data. Optimal patient selection criteria have not yet been established.

**Prognostic implication of lower LVEF and higher PAP:**
As reported by Solomon, *et al*, the prognosis of heart failure is strongly associated with the preservation of LVEF. In patients with heart failure with reduced LVEF, MR coexistence is associated with the unfavorable outcome even if MR severity is mild. LVEF is a surrogate of the severity of heart failure, and patients with advanced heart failure accompanied by reduced LVEF often have LV remodeling refractory to any pharmacological and mechanical LV unloading. Consistently, 4 patients with low LVEF (<29%) experienced heart failure readmissions following a MitraClip procedure, despite no MR recurrence.

Secondary pulmonary hypertension due to left-side heart failure is also associated with a poor prognosis due to biventricular failure. Of note, patients with reactive pulmonary hypertension are often refractory to any pharmacological and mechanical therapies. In this study, PVR significantly improved after the procedure irrespective of the degree of mean PAP and LVEF. On the contrary, PVR in the chronic phase significantly worsened in patients with baseline high PAP and reduced EF, whereas it tended to improve in those with baseline normal PAP or higher LVEF (Figure 2B). Persistent pulmonary hypertension might worsen right heart function, systemic congestion, and multi-organ dysfunction.

Excessively remodeled pulmonary artery and LV, which are indicated by mean PAP > 21 mmHg and LVEF < 29%, may not recover despite the successful regulation of MR using the MitraClip system. However, even in the lower LVEF group, LVEF did not decrease immediately after the procedure, and the MitraClip procedure may be at least safer than the surgical procedure.

**Future concerns:** In advanced heart failure patients with severe MR, left ventricular assist device (LVAD) implantation is known as a strong therapeutic option. LVAD implantation should be a good option, particularly for patients with severe MR and advanced heart failure assigned to the INTERMACS profile 1-3, if applicable. If patients have a high risk for such surgical therapies, the MitraClip system should at least be considered. Our findings would be useful for risk stratification and prognostic prediction.

LVAD implantation for less sick cohorts, i.e., those with INTERMACS profile 4-7, is controversial. Several large-scale studies including the ROADMAP trial49 and REVIVE-IT trial40 may not support an aggressive indication of LVAD therapy in such less sick cohorts given the frequent readmissions due to device-related comorbidities. Nevertheless, a certain number of cohorts, such as a patient with severe ventricular tachyarrhythmia or elevated B-type natriuretic peptide, still might be good candidates for LVAD implantation. Among the patients with severe MR and advanced heart failure assigned to INTERMACS profile 4-7, those with PAP > 21 mmHg and LVEF < 29%, a high-risk group in this study, may also be good candidates for LVAD implantation, given that they are expected to have worse clinical outcomes following a MitraClip procedure.

**Limitations:** Several limitations of the present study should be addressed. First, this is a retrospective single-center analysis among a small size cohort. We constructed a multivariable model just using two parameters given the small sample size and event number. We performed the ROC analyses to propose prognosis-associated cutoffs for each risk factor, instead of utilizing well-known cutoffs such as 40% for LVEF. Any other risk factors or more appropriate cutoffs may be found in larger-scale studies. Further studies with a larger-scale sample size should be conducted to validate our findings and further investigate a better therapeutic strategy using the MitraClip procedure. We believe that this study should be a proof-of-concept for conducting such future studies.

**Conclusion**
Although limited for the aforementioned reason, this study suggests that pre-procedural mean PAP may be useful for predicting post-procedural events as well as LVEF. Given our findings, a detailed mechanism should be considered and a treatment strategy for heart failure with reduced ejection fraction patients co-existing MR should be concerned.

**Disclosure**
Conflicts of interest: None.

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