Association of heart failure duration with clinical outcomes after transcatheter mitral valve repair for functional mitral regurgitation

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Abstract

Background: Little is known about the association of heart failure (HF) chronicity with clinical outcomes after transcatheter mitral valve repair (TMVR) for functional mitral regurgitation (MR).

Methods: From January 2011 to March 2019, consecutive patients with functional MR who underwent a MitraClip procedure were analyzed. The patients were divided into two groups according to HF duration—those with duration ≤18 months and those with >18 months. The primary outcome measure was a composite of all-cause mortality and re-HF rehospitalization within 1 year after the procedure. These outcomes were also assessed separately. A Cox proportional hazard model was conducted for investigating the association of HF duration with the primary outcome.

Results: A total of 208 patients were analyzed. Patients with HF duration >18 months had a higher rate of the primary outcome compared to those with HF duration ≤18 months (38.1 vs. 19.0%, log-rank p = .003). A longer duration of HF was associated with an increased risk of the primary outcomes (adjusted-HR of >18 months, 2.12 95% CI, 1.14–4.19; p = .03; adjusted-HR (hazard ratios) for 1 year increase, 1.05; 95% CI, 1.02–1.09; p = .004). The association of HF duration with the primary outcomes showed a steep rise during the first 2 years of HF duration and progressive increase after 5 years.

Conclusions: A longer HF duration before TMVR was associated with an increased risk of all-cause mortality or HF rehospitalization. HF duration can be used for the risk stratification marker in patients undergoing TMVR for functional MR.

KEYWORDS
clinical prognosis, functional mitral regurgitation, heart failure duration, mitraclip
1 | BACKGROUND

In patients with heart failure (HF), functional mitral regurgitation (MR) is a consequence of cardiac remodeling. The geometrical malformation of the papillary muscles and chordae results in malcoaptation of leaflets. The functional MR increases the risk of mortality and facilitates cardiac remodeling. Transcatheter mitral valve repair (TMVR) has been used for patients with symptomatic, medically refractory, functional MR. However, the prognostic benefit of TMVR for functional MR remains unclear. The current landmark trials (MITRA-FR and COAPT trials) have demonstrated inconsistent findings in reduction of mortality and hospitalization for patients with HF. The conflicting evidence may be attributable to intrinsic myocardial damage suggested by the differences in left-ventricular (LV) volumes between the patients in the trials. However, due to its load-dependent nature, LV volumes may overestimate the degree of myocardial injury. Furthermore, a direct measure of myocardial injury may be impractical in clinical practice. In this context, parameters that are surrogate for internal myocardial damage are therefore needed.

HF duration, which is a prognostic marker in patients with HF, can be used as a surrogate of the degree of cardiac remodeling and intrinsic myocardial damage. Patients with an extended duration of HF are more likely to have progressive myocardial injury due to long-standing neuroendocrine activation. Nevertheless, little is known about the association of HF duration with clinical prognosis after TMVR in patients with functional MR.

To address this gap in the literature, we investigated the association between HF duration and clinical outcomes after TMVR in patients with functional MR.

2 | METHODS

2.1 | Study design and setting

This is a retrospective cohort study wherein data was extracted from the University of Bonn Heart Center, Germany, from January 2011 to March 2019. At the University of Bonn Heart Center, patients were evaluated for the treatment of MR by the institutional heart team and referred to TMVR when they were deemed to be inoperable or had a high-surgical risk. TMVR was performed in symptomatic patients despite guideline-directed medical therapy. The TMVR procedure with the MitraClip system has been previously described. All procedures were performed under general anesthesia with guidance given by fluoroscopy and transesophageal echocardiography. This study was approved by the ethics committee of the University of Bonn and was conducted in accordance with the Declaration of Helsinki. All patients participated in the study after written informed consent was obtained.

2.2 | Study participants

We included consecutive patients with functional MR who underwent TMVR with a technical success by using the MitraClip system. According to the Mitral Valve Academic Research Consortium (MVARC) criteria, technical success was assessed upon exit from the catheterization room and was defined as a procedure that met all of the following conditions: the absence of procedural mortality; successful access, delivery, and retrieval of the device delivery system; successful deployment and correct positioning of the intended device; and absence of emergency surgery or reintervention related to the device or access procedure.

2.3 | Exposure

The exposure was HF duration, which was calculated from the first HF hospitalization to the hospitalization for TMVR. HF hospitalization was defined as hospitalization due to HF from any cause according to prior publications. Medical records were used by the study investigators to determine the date of the diagnosis for each case. Then, patients were divided into two groups by the HF duration (≤18 or > 18 months), based on a previous cutoff value.

2.4 | Echocardiographic assessment

Echocardiography was performed according to the current American and European guidelines. The severity of MR was classified as grade 0: none, 1+: mild, 2+: moderate, 3+: moderate-to-severe, and 4+: severe. All assessments were performed by two cardiologists who were blinded to the present study.

2.5 | Clinical outcomes

The primary outcome measure was a composite of all-cause mortality and rehospitalization due to HF within 1 year after the TMVR procedure. We also assessed each outcome separately. Outcome data were collected prospectively during planned hospital visits or telephone interviews with the patients' general practitioners and family.

2.6 | Statistical analysis

Baseline characteristics were compared between groups. Continuous variables with a normal distribution were compared by using a Kruskal–Wallis test and reported as the mean ± SD. In contrast, those with a non-normal distribution were analyzed by using the Mann–Whitney U test. Noncategorical variables were compared by using the Pearson chi-square test or Fisher exact test, as appropriate, and were presented as frequencies and percentages. We represented event-free survival curves using the Kaplan–Meier method, according to HF duration (≤18 or > 18 months). Then, Cox proportional hazard models were conducted to calculate the hazard ratios (HR) and 95% confidence intervals (CI) of the group with HF duration >18 months for the outcomes, in comparison with the group with HF duration.
≤18 months. The variables for an adjustment were age, sex, coronary artery disease, LV ejection fraction (LVEF), and STS score based on a priori knowledge.16–18

To examine the robustness of our inference, we performed several sensitivity analyses. First, we performed a survival analysis with different cutoffs of HF duration (≤12, 13–60, and ≥61 months).11,19

TABLE 1  Baseline characteristics in patients according to the duration of heart failure

|                        | HF duration ≤18 months n = 89 | HF duration >18 months n = 119 | p value |
|------------------------|-------------------------------|--------------------------------|---------|
| Age (years)            | 76 ± 9                        | 76 ± 7                         | .63     |
| Male sex               | 46 (51.7)                     | 90 (75.6)                      | <.001   |
| Body mass index (kg/cm²)| 27.1 ± 5.3                    | 26.6 ± 5.5                     | .53     |
| Comorbidities          |                               |                                |         |
| Hypertension           | 69 (77.5)                     | 81 (68.1)                      | .16     |
| Diabetes mellitus      | 27 (30.3)                     | 39 (32.8)                      | .76     |
| Atrial fibrillation    | 66 (74.2)                     | 87 (73.1)                      | .99     |
| Coronary artery disease| 45 (50.6)                     | 85 (71.4)                      | .002    |
| Prior myocardial infarction | 27 (30.3)           | 68 (57.1)                      | <.001   |
| Chronic obstructive pulmonary disease | 18 (20.2) | 18 (15.1)                      | .36     |
| Chronic kidney disease | 64 (71.9)                     | 90 (75.6)                      | .63     |
| Prior coronary artery bypass graft | 14 (15.7) | 51 (42.9)                      | <.001   |
| Prior CRT              | 5 (5.6)                       | 23 (19.3)                      | .008    |
| STS score (%)          | 4.8 ± 4.5                     | 5.9 ± 4.1                      | .07     |
| New York heart association scale III/IV | 68 (76.4) | 94 (79.0)                      | .74     |
| Systolic blood pressure (mmHg) | 122.8 ± 21.6          | 116.6 ± 17.3                   | .10     |
| Diastolic blood pressure (mmHg) | 75.0 ± 11.5          | 69.7 ± 10.7                    | .02     |
| Heart rate (bpm)       | 72.3 ± 15.6                   | 73.6 ± 14.1                    | .86     |
| Laboratory findings    |                               |                                |         |
| Hemoglobin (g/dl)      | 12.2 ± 1.8                    | 11.8 ± 1.9                     | .15     |
| NT-pro-BNP (pg/ml)     | 3,476 (1749, 6,779)           | 5,191 (2,934, 11,803)          | .03     |
| Estimated GFR (ml/min/1.73m²) | 44.2 ± 17.3               | 43.4 ± 18.5                    | .74     |
| Transthoracic echocardiography at enrollment |                                      |                                |         |
| LV end-diastole volume (ml) | 142.1 ± 59.2               | 195.1 ± 82.6                   | <.001   |
| LV end-diastole volume index (ml/m²) | 74.6 ± 32.5               | 101.8 ± 38.7                   | <.001   |
| LV end-systole volume (ml) | 86.5 ± 50.5               | 130.1 ± 67.9                   | <.001   |
| LV end-systole volume index (ml/m²) | 44.8 ± 26.7               | 680 ± 31.1                     | <.001   |
| LV ejection fraction (%)| 43.7 ± 15.3                  | 34.1 ± 12.0                    | <.001   |
| LA volume (ml)         | 109.3 ± 59.8                 | 116.9 ± 52.6                   | .42     |
| MR 4+                  | 37 (42.0)                    | 66 (56.4)                      | .049    |
| Effective regurgitation orifice area (cm²) | 0.27 ± 0.11              | 0.33 ± 0.14                    | .009    |
| Proximal isovelocity hemispheric surface area (cm) | 0.69 ± 0.16              | 0.79 ± 0.17                    | <.001   |
| Vena contracta (cm)    | 0.61 ± 0.14                  | 0.75 ± 0.24                    | <.001   |
| TRPG (mmHg)            | 42.6 ± 15.0                  | 45.1 ± 14.4                    | .27     |
| Medications upon discharge |                                       |                                |         |
| Beta blocker           | 74 (86.0)                    | 100 (86.2)                     | .99     |
| Angiotensin converting enzyme inhibitor | 39 (45.3)              | 59 (50.9)                      | .48     |
| Angiotensin II receptor blocker | 28 (32.6)           | 28 (24.1)                      | .21     |
| Mineralocorticoid receptor antagonist | 56 (65.1)       | 71 (61.2)                      | .66     |

Note: Continuous variables: mean ± SD or median (IQR), categorized variables: n (%).
Abbreviations: CRT, cardiac resynchronization therapy; GFR, glomerular filtration ratio; HF, heart failure; ICD, implantable cardioverter defibrillator; IQR, interquartile range; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; LV, left ventricular; TRPG, tricuspid regurgitation pressure gradient.
Second, to assess the exposure-response relationship between HF duration and the incidence of the composite outcomes, a locally weighted error sum of squares (Lowess) curve was used. Third, we also depicted the association of HF duration with LVEF and LV end-systolic volume (LVESV).19,20

Furthermore, we performed a propensity score (PS) matching and stabilized inverse probability weighting (IPW), with a random forest imputation method for missingness.

First, since PS analysis requires no-missingness in data, we imputed missing values using a random forest method.21 The missingness in each variable is summarized in Supplemental Table 1. Random forest imputation is a nonparametric algorithm that accommodates nonlinearities and interactions and does not require the specification of a particular parametric model. With this approach, single-point estimates were generated by random draws from independent normal distributions centered on conditional means predicted with random forest. Random forest utilizes bootstrap aggregation of multiple regression trees to reduce the risk of overfitting and combines the estimates from many trees. Missingness was imputed using baseline characteristics and echocardiographic data.

Second, as suggested by the reviewer, we performed 1:1 PS matching using a caliper of the width of 0.25 of the standard deviation of the PS.22 The PS was calculated using age, sex, coronary artery disease, prior myocardial infarction, prior CABG, diastolic BP, prior cardiac resynchronization therapy, STS score, LVEF, LV end-diastolic volume, LV end-systolic volume, MR 4+, vena contract, PISA, and ERO, based on the comparative analysis of baseline characteristics and a priori knowledge (2–4).

Last, accounting for the small sample size of the current study, we used stabilized IPW methods to estimate the effect of HF duration on the outcomes. Weighting subjects by the inverse probability to have an exposure (HF duration >18 months) creates a synthetic sample in which the exposure is independent from measured baseline covariates. Although conventional IPW enables us to obtain unbiased estimates of the exposure’s effect on each outcome, subjects with a very low or high PS can increase the variability of the estimated effects. Stabilized IPW addresses this issue and directly estimates both the main effect and its variance from conventional regression models.

All statistical analyses were performed using EZR version 1.37 (Saitama Medical Center, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Austria).23 Two-tailed p values < .05 were considered statistically significant.

3 RESULTS

There were 215 patients with data available on HF duration in the proposed study period. According to the MVARC criteria, 208 of these patients achieved technical success and were eligible for the analysis (Supplemental Figure 1). Overall, the mean age was 78 years old and 65% of patients were male. The mean LVEF was 38.2%, LVESV was 62.7 ml, and effective regurgitation orifice area was 0.30 cm².

Baseline characteristics were listed in Table 1. Patients with longer HF duration (>18 months: n = 119) were more often male, had coronary artery diseases, larger LV volume, lower LVEF fraction, higher STS score, and more elevated NT-pro-brain natriuretic peptide, as compared to patients with shorter HF duration (≤18 months: n = 89). Supplemental Table 2 lists the procedural findings. There were no significant differences in the number of clips implanted or the post-procedural TMPG or residual MR grades between the groups.

TABLE 2 Cox proportional hazard regression analysis for primary outcome

| Outcome                  | HF duration >18 months % (95% CI) | HF duration ≤18 months % (95% CI) | Unadjusted HR (95% CI) | p value | Adjusted HR (95% CI) | p value |
|--------------------------|----------------------------------|----------------------------------|------------------------|--------|----------------------|--------|
| Primary outcome          | 38.1 (29.5–48.2)                 | 19.0 (11.7–30.0)                | 2.42 (1.32–4.45)       | .004   | 2.12 (1.14–4.19)     | .03    |
| All-cause mortality      | 22.5 (15.6–31.7)                 | 7.5 (3.4–16.0)                 | 3.11 (1.27–7.61)       | .01    | 3.12 (1.12–8.69)     | .03    |
| HF hospitalization       | 21.4 (14.2–31.7)                 | 10.7 (5.3–21.3)                | 2.18 (0.95–4.99)       | .07    | 1.64 (0.58–4.63)     | .35    |

Abbreviations: CI, confidence interval; HF, heart failure; HR, hazard ratio.
3.1 | Clinical outcomes

During the one-year follow-up period with a median follow-up of 520 days (IQR 100–1,049 days), 54 patients (26%) achieved the composite outcome (30 patients died, and 27 were rehospitalized due to HF). Patients with longer HF duration (>18 months) had a significantly higher rate of the primary outcome as compared with patients with shorter HF duration (≤18 months) (38.1 vs. 19.0%, log-rank \( p = .003 \); Figure 1). Likewise, in the Cox proportional hazard model, a longer HF duration was significantly associated with an increased risk of the primary outcome (adjusted HR, 2.12; 95% CI, 1.14–4.19; \( p = .03 \)) (Table 2).

3.2 | Sensitivity analysis

Similar to the findings for the primary analysis, patients with a longer HF duration had higher mortality compared with those with a shorter HF duration (22.5 vs. 7.5%, log-rank \( p = .009 \)). This association remained significant even after an adjustment for the predefined covariates (adjusted HR, 3.12; 95% CI, 1.12–8.69; \( p = .03 \)) in the multivariate model. With a limited sample size, a similar association was observed for rehospitalization due to HF (21.4 vs. 10.7%, log-rank \( p = .06 \); and adjusted HR, 1.64; 95% CI, 0.58–4.63; \( p = .35 \)).

Supplemental Table 3 lists the results of survival analysis using different cutoffs (≤12, 13–60, and ≥61 months). Patients with HF duration ≥61 months had the highest rates of the primary outcome, 1 year mortality, or rehospitalization due to HF. In the Cox proportional hazard model, the directions of the association between longer HF duration and increased risk of outcomes were consistent. A lowess curve for the relationship between the composite outcome and HF duration is illustrated in Figure 2. A steep elevation was observed in the first 2 years, followed by a decrease until 5 years and a progressive increase thereafter. As a whole, longer HF duration was associated with an increased risk of the primary outcome (HR for one-year increase, 1.05; 95% CI, 1.02–1.09; \( p = .004 \)) after adjusting for the predefined covariates.

Furthermore, we performed 1:1 PS matching to address the differences in baseline characteristics. The kernel density of PS before and after matching is shown in Supplemental Figure 2. Baseline characteristics after PS matching and the standardized differences of variables that were used for calculating PS are shown in Supplemental Table 4. In the PS-matched cohort, longer HF duration was significantly associated with a higher risk of the primary outcome (Odds ratio [OR], 3.20; 95% CI, 1.12–9.19; \( p = .03 \)). When assessing mortality and rehospitalization separately, longer HF duration was likely associated with a higher risk of mortality OR, 3.47; 95% CI 0.88–13.76, \( p = .08 \) and of rehospitalization (OR, 2.57; 95% CI, 0.62–10.6; \( p = .19 \)) but not statistically significant.
Last, we used stabilized IPW methods to estimate the effect of HF duration on the outcomes. In this analysis, longer HF duration was significantly associated with an increased risk of the primary outcome (OR, 4.20; 95% CI 1.46–12.08, p = .008). When assessing the composite outcome separately, longer HF duration was significantly associated with worse mortality (OR, 2.56; 95% CI 1.12–5.84, p = 0.03), but not for rehospitalization (OR, 1.62; 95% CI, 0.55–4.76; p = 0.38).

### 3.3 Relationship of echocardiographic LV parameters with HF duration

A lowess curve for the relationship between LVEF and HF duration is illustrated in Figure 3a. A smooth decline was observed in the first 10 years, followed by an unstable plateau toward the end. Figure 3b depicts the relationship between LVESV and HF duration. A mild increase was observed in the first 10 years, followed by an unstable plateau thereafter.

### 4 DISCUSSION

In this analysis of patients with functional MR who underwent TMVR, we found that a longer HF duration was associated with an increased risk of adverse outcomes during the one-year follow-up period after TMVR. The observed association persisted across several different analytical assumptions. We found that the incidence of the outcome increased in the first 2 years of HF duration, moderately decreased in the following years, and increased progressively thereafter. To the best of our knowledge, our study is the first to investigate the association of HF chronicity with adverse outcomes after TMVR in patients with functional MR.

#### 4.1 Intrinsic myocardial damage in patients with functional MR

Intrinsic myocardial damage may be the key in predicting patient prognosis after TMVR based on the findings from the recent two trials, MITRA-FR, and COAPT trials.\(^6\) The MITRA-FR trial reported no reduction in mortality or rehospitalization after TMVR compared to guideline-directed medical therapy only.\(^5\) In contrast, the COAPT trial reported a significant decrease in those outcomes.\(^7\) As patients in the MITRA-FR trial had a larger LV volume compared to those in the COAPT trials, these conflicting results might reflect the different extent of the intrinsic myocardial damage between the trials: patients with profound myocardial damage might profit less than those without. The gold-standard for assessing the intrinsic myocardial damage is cardiac magnetic resonance imaging (MRI).\(^17\)\(^18\) However, the use of cardiac MRI in the clinical setting might be impractical due to a prior-implanted device or comorbidities. Furthermore, due to the load-dependent nature of LV function,\(^19\) LVEF or LV volumes are expected to underestimate the degree of the internal myocardial injury. In this context, parameters that are surrogate for the internal myocardial injury are therefore needed.

#### 4.2 HF duration and myocardial damage

We found that a longer HF duration was associated with an increased risk of adverse outcomes after TMVR. Our findings are in line with those in earlier studies on chronic HF, which showed that the risk of the cardiovascular outcomes increased according to HF duration.\(^11\)\(^19\) Suffering from HF accompanies myocardial remodeling due to neuroendocrine activation, calcium-handling defects, or beta-adrenergic signal transduction.\(^24\)\(^25\) Besides, coronary artery diseases also cause myocardial damage,\(^26\) and myocardial ischemia acts on the pathophysiology of cardiac remodeling,\(^26\) which may further contribute to the association between longer HF duration and the increased risk of the outcome.

In the relationship between the chronicity of HF and the outcome, a steep elevation was observed in the first 2 years of HF duration. This association may be due to the linking of HF hospitalization to an increased risk of cardiovascular events.\(^27\) Following a moderate decrease might be due to the up-titration of medical therapy. A progressive increase was observed after 5 years. Profound myocardial damage caused by long-lasting HF may be responsible for this increase. However, LVEF and LVESV showed a plateau in the extended period of HF. Our finding is in line with those in earlier cohort studies on the advanced HF stage.\(^12\)\(^28\) The extent of myocardial damage, such as myocardial fibrosis, is independent of LVEF or LV volumes and has a negative impact on prognosis.\(^29\)

Consequently, our findings suggest that HF duration, which reflects the intrinsic myocardial damage, is an essential factor in the prognosis after TMVR. Therefore, HF duration might help to identify patients who will benefit from TMVR for functional MR.

#### 4.3 Limitations

Our study has several potential limitations. First, this is a single-center, retrospective study with limited sample size. Nevertheless, consistent findings among several sensitivity analyses support the validity of the association of interest. Second, there might be misclassification of HF duration, as the initial date of HF diagnosis was retrospectively confirmed by study investigators according to each patient’s medical history. Yet, the observed association persisted across several analysis using different cutoffs. Therefore, this approach is acceptable and may be generalized to clinical practice. Third, since the HF duration was calculated based on medical history and did not indicate the time period that the patients were suffering from MR, we cannot interpret the current findings to be the “optimal timing to treat MR.” Fourth, we do not have data on the duration of optimal medical therapy prior to TMVR.

### 5 CONCLUSIONS

In patients who underwent TMVR for functional MR, a longer duration of HF was associated with an increased risk of a composite of all-cause mortality and rehospitalization due to HF within 1 year after the TMVR procedure. HF duration, which reflects the intrinsic
myocardial damage, can be used as a risk indicator for patients who will be treated with TMVR.

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CONFLICT OF INTERESTS
Grube E, Werner N, Nickenig G, and Sinning JM report having received speaker honoraria and research grants from Medtronic, Boston Scientific, Edwards Lifesciences, and Abbott. Grube E has received lecture or proctoring fees from Boston Scientific and Medtronic. Weber M has received lecture or proctoring fees from Abbott, Boehringer-Ingelheim, Edwards Lifesciences, Neochord, Pfizer, and Servier. The other authors report no conflicts of interest.

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SUPPORTING INFORMATION
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