Received: 1 March 2020 | Revised: 23 April 2020 | Accepted: 26 May 2020

DOI: 10.1002/ccd.29068

ORIGINAL STUDIES

WILEY

Predictors of short- and long-term outcomes of patients undergoing transcatheter mitral valve edge-to-edge repair

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Abstract

Objectives: Transcatheter mitral valve repair (TMVR) by edge-to-edge therapy is an established treatment for severe mitral valve regurgitation (MR).

Background: Symptomatic and prognostic benefit in functional MR has been shown recently; nevertheless, data on long-term outcomes are sparse.

Methods and results: We analyzed survival of patients treated with isolated edge-to-edge repair from June 2010 to March 2018 (primarily combined edge-to-edge repair with other mitral valve interventions was excluded) in a retrospective monocentric study. Overall, 627 consecutive patients (47.0% females, 78.6 years in mean) were included. Leading etiology was functional MR (57.4%). Follow-up regarding survival was available in 97.0%. While 97.6% were discharged alive, 75.7% were alive after a 1-year, 54.5% after 3-year, 37.6% after 5-year and 21.7% after 7-year follow-up. Higher logistic Euroscores and comorbidities such as COPD and renal insufficiency were associated with higher in-hospital and 1-year mortality. Importantly, in-hospital survival increased over the years.

Conclusions: With the present study we established high survival rates at discharge and after 1 year of patients treated with TMVR. This goes along with high implantation numbers, increased interventional experience and a better in-hospital survival over the years. Long-term mortality in turn was substantially influenced by comorbidities.

KEYWORDS

mitral regurgitation, mitral valve repair, multidisciplinary heart team, survival

Abbreviations: ASE, American Society of Echocardiography; CI, confidence interval; EACVI, European Association of Cardiovascular Imaging; FDA, (US) Food and Drug Administration; IQR, interquartile range; LVEF, left ventricular ejection fraction; MR, mitral valve regurgitation (DMR: degenerative, FMR: functional); MVARC, mitral valve academic research consortium; OR, odds ratio; TMVR, transcatheter mitral valve repair.

Martin Geyer and Karsten Keller contributed equally and should both be considered as first authors.

1 | INTRODUCTION

Mitral valve regurgitation (MR) has an age-dependent prevalence of 1%–2% in the general population and over 10% in individuals older than 75 years.[1] Due to a different etiology and pathophysiology, functional (FMR) has to be discriminated from degenerative MR (DMR), e.g., using the classification by Carpentier.[2] FMR is in general a consequence of concomitant heart failure and the high-grade MR determines and limits individual prognosis.[3,4] Since only about half of patients with severe MR are eligible for surgical treatment,[5] percutaneous minimally invasive techniques for transcatheter mitral valve repair (TMVR) are increasingly used over the last years. A remarkable variety of approaches for interventional therapy of MR have been developed and several of these devices have been introduced into daily treatment routine. Abbott MitraClip (Abbott Vascular, Santa Clara, California) is implanted as a so-called "edge-to-edge"-therapy and represents the most established percutaneous treatment modality of TMVR up to now. The device has been approved with the European CE-Mark in 2008 for both DMR and FMR as well as by the FDA in 2013 for DMR. A study based on official remuneration data of the Federal Statistical Office of Germany reported that 3.35 per 100 000 citizens received TMVR annually by edge-to-edge therapy during 2011–2015 in Germany with an increasing usage of this technique during the observational period.[6]

Recently, results of two large randomized prospective multicenter trials on the effect of an edge-to-edge repair for FMR have been published with in part divergent results: while the US COAPT-trial demonstrated a prognostic and symptomatic benefit by interventional compared to optimal medical treatment,[7] the French MITRA-FR failed to show significant differences regarding the endpoints re-hospitalization and mortality.[8] Furthermore, evidence on long-term effects of TMVR by MitraClip is still widely lacking. TRAMI, a German multicenter retrospective registry comprising more than 700 patients undergoing MitraClip-therapy, identified procedural failure as strongest predictor of 1-year mortality.[9] After a follow-up of 4 years, long-term outcome was mainly influenced by the left ventricular ejection fraction (LVEF), but also by non-cardiac comorbidities like renal insufficiency.[10] A large German study comprising inpatient-data on 13,575 subjects with TMVR by edge-to-edge repair identified heart failure and periprocedural complications (stroke, endocarditis, pulmonary embolism, pericardial effusion) as relevant prognostic factors for in-hospital mortality.[6]

The University Medical Center Mainz is one of the largest centers for TMVR worldwide with an implantation experience of more than 1000 treated patients. The objectives of the present study were (a) to investigate in-hospital and one-year mortality in a large longitudinal monocentric retrospective cohort, (b) to analyze trends in the baseline parameters (especially age and comorbidities) of the patients, (c) to detect potential temporal trends in short- and long-term mortality over the years in this cohort, and (d) to identify predictors of prognosis.

2 | METHODS

Our analysis included patients consecutively treated for MR (regardless the underlying pathomechanism) with edge-to-edge repair at our University-Center for Cardiology between June 2010 and March 2018. All patients were treated with MitraClip classic or NT before the introduction of the latest generation (NTR/XTR) of the device. Patients primarily undergoing a combination with other forms of TMVR simultaneously with edge-to-edge repair were excluded. All subjects were adult individuals (≥18 years) with moderate to severe or severe MR despite optimal medical treatment, including cardiac resynchronization therapy and estimated to be at high-risk for surgery by an interdisciplinary board (Heart Team).

The individual risk for alternative surgical treatment was assessed by scoring systems (eg, Logistic Euroscore), as well as other individual factors such as frailty and comorbidities. Patients were invited and recommended to undergo follow-up visits at 1 and 12 months at our center, encompassing clinical and echocardiographic examinations as well as laboratory tests. Long-term survival or date of death, respectively, were assessed based on entries in patients' records and an enquiry at the Rhineland-Palatinate bureau of vital statistics due to 8th March 2018.

2.1 | Study endpoint

Primary outcome was all-cause-mortality, stratified for the following time-periods: in-hospital stay, 1-year and long-term follow-up.

2.2 | Definitions

In accordance to the recommendations by the Mitral Valve Academic Research Consortium/MVARC[11]), technical success was defined as ability to deploy the device as intended (no failure of device placement due to anatomical or other operator-reported reasons, for example, resulting relevant mitral stenosis after grasping, leading to removal of the device and abortion of the procedure) and successful retrieval of the delivery system without periprocedural mortality or need of emergency surgery or intervention. MR was quantified in four grades, according to European guideline recommendations[12]: 0 for no or trace, I for mild, II for moderate, and III for severe MR. Renal insufficiency was defined by a glomerular filtration rate < 60 mL/min kg. Pulmonary hypertension was determined by invasive measurements or echocardiographic high probability by RV/RA-gradient, according to the current guidelines.[13] Obesity was defined as BMI ≥ 30 kg/m^2. Echocardiographic left- and right-ventricular analysis and quantification were based on transthoracic echocardiography measurements and evaluated in accordance to ASE/EACVI recommendations.[14]

Conditions recorded as major adverse in-hospital events were: development of acute kidney injury, myocardial infarction, pulmonary embolism, necessity for further mitral surgery, stroke and

hemodynamically relevant pericardial effusion (for details, see also recommendations by MVARC[11]).

2.3 | Ethical aspects

The study involved only anonymized, retrospective analysis of diagnostic standard data and was approved by the local committee on human research.

2.4 | Statistical analysis

Descriptive statistics were provided with median and interquartile range (IQR), or absolute numbers and percentages. Continuous variables were compared using the Wilcoxon-Whitney *U* test and categorical variables with Fisher's-exact or chi^2-test, as appropriate. Linear regressions were computed to investigate the trend regarding an increase in annual numbers of patients. Results were presented as beta (β) and 95%-confidence intervals (CI). Logistic regression models were calculated to examine the impact of patients' characteristics as well as examination results on in-hospital mortality. Results were presented as odds ratios (OR) and 95% CI. Analyses were performed in a univariate and a multivariate manner: Cox regression models were computed to examine the impact of patients' characteristics as well as examination results on the 1-year mortality. Results were presented as Hazard Ratios (HR) with 95%CI in univariate and in multivariate manner adjusted for adjustment (I) age and sex as well as for adjustment (II) age, sex, New York Heart Association (NYHA) class, LVEF, tricuspid valve regurgitation, coronary artery disease, previous myocardial infarction, chronic kidney disease, and chronic obstructive pulmonary disease (COPD). The software SPSS (version 23.0; SPSS Inc., Chicago, Illinois) was used for computerized analysis. *P*-values of <.05 (two-sided) were considered to be statistically significant.

3 | RESULTS

3.1 | Baseline characteristics and enrolment (Figure 1)

Between 09th June 2010 and 08th March 2018, 725 consecutive patients underwent percutaneous edge-to-edge-therapy. Ninety subjects (12.4%) had primarily undergone TMVR by a simultaneous combination of edge-to-edge repair with other forms of interventional treatment (eg, interventional annuloplasty or chordal reconstruction) at the index procedure; furthermore, eight patients (1.3%) were not included due to technical failure (resulting mitral stenosis, leading to abortion of clip implantation in six patients; hemodynamic instability under general anesthesia before insertion of the transseptal sheath in one patient, pericardial tamponade before introduction of the implantation and peri-interventional death in one patient).

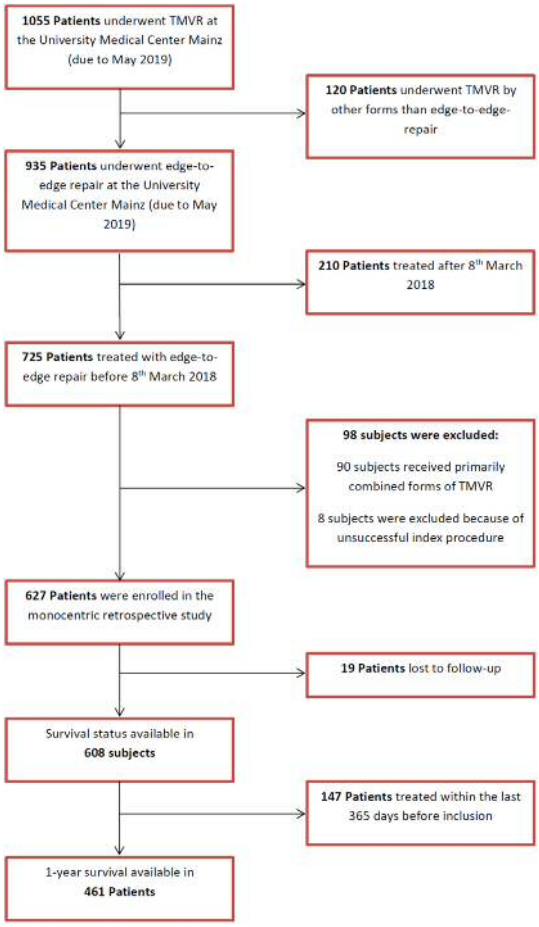

FIGURE 1 Flow diagram of the study population. Flow diagram of study enrolment (for details, see text)

The remaining 627 patients were in mean 78.6 ± 7.3 years old (median 79.1 [74.2/84.2]; 88.2% >70 years) at the time of procedure with a nearly balanced proportion of females (47.0%). Predominant etiology was FMR in 57.4% (DMR: 30.6%, mixed etiology: 12.0%); average logistic Euroscore was 29.6% ± 16.9 (median 26.0 [18.3/38.5]). LVEF was in mean moderately impaired (41.5% ± 13.4; median 42.0 [30.0/55.0]). MR before the procedure was classified as severe grade in 570 (91.4%) and as moderate in 54 (8.6%) cases. The annual numbers of TMVR using an edge-to-edge approach increased continually starting from 20 implantations in 2010 to 129 in 2017 (β 0.06 [95%CI 0.05–0.07], P < .001, Figure 2). In mean, 1.5 ± 0.6 (median 1.0 [1.0/2.0]) MitraClip-devices were implanted during each index procedure.

3.2 | Survival at discharge and at 1 year

On 8th March 2018, survival status was available in 608 patients (97.0%). Of these, in 461 (73.5%) time to follow-up was >1 year. Figure 3 visualizes the results of the long-term survival course of our study patients treated. While 97.6% of the patients were discharged

alive, 75.7% lived after 1-year, 54.5% after 3-year, 37.6% after 5-year, and 21.7% after 7-year follow-up.

Although the proportion of patients aged >70 years increased from 70.5% in the years 2010/2011 to 95.9% in the years 2017/2018 ($P < .001$; median age was 75.2 [67.7/80.1] in 2010/2011 and 80.6 [76.6/85.3] in 2017/2018), in-hospital mortality decreased substantially from 9.1% in 2010/2011 to 0.6% in 2017/2018 ($P = .001$) despite maintaining a high-risk profile in average over the whole study period: mean logistic Euroscore was 29.7% with a decrease to lower mean values (36.2% in 2010/11 vs 25.9% in 2017/18, $P = .001$). For details, see Figures 4 and S1.

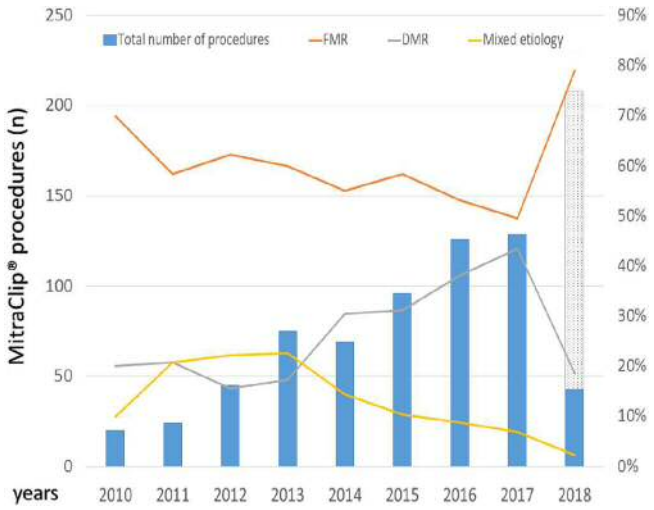

FIGURE 2 Annual total numbers of procedures. Annual total numbers of patients included in the study (blue bars) receiving edge-to-edge therapy (combined procedures excepted) stratified for etiologies (FMR, orange line; DMR, gray line; mixed etiology, yellow line). For a better understanding of the development of implantation numbers, the dotted bar (year 2018) shows the procedures, which were done in the year 2018 after the end of the enrolment period of this analysis at the University Medical Center Mainz

3.3 | Differences in baseline characteristics of 1-year survivors vs non-survivors

Patient characteristics are shown in Table 1. Non-survivors of the first year were of similar age in comparison to survivors. As expected, logistic Euroscore was significantly higher in non-survivors (37.0% [24.5/51.2] vs 24.0% [17.7/34.7], $P < .001$). No differences could be identified regarding the underlying etiology of MR, the number of implanted clips or gender. Comparing baseline characteristics, severe dyspnea (NYHA III/IV: 95.0% vs 86.6%, $P = .021$) before the procedure was recorded more often in non-survivors. While prevalence of cardiovascular risk factors was similar, COPD (21.4% vs 12.9%, $P = .028$), renal insufficiency (67.9% vs 43.1%, $P < .001$), coronary artery disease (78.6% vs 60.9%, $P = .001$) and history of myocardial infarction (38.4% vs 22.9%, $P = .001$) were found in a higher percentage in non-survivors.

Notably, the groups did not differ significantly in pre-interventional heart failure medications as well as most of the assessed echocardiographic parameters, except for lower LVEF (35.0 [27.5/50.0] vs 40.0 [30.0/55.0], $P = .025$) and higher grades of tricuspid regurgitation ($P = .022$) in non-survivors (Table 1). Furthermore, average baseline levels of creatinine, brain natriuretic peptides (BNP) and high-sensitive Troponin I (hsTnI) were all higher in non-survivors than in survivors.

3.4 | Baseline predictors of in-hospital death

By calculating logistic regressions, a higher logistic Euroscore (OR 1.05 [95%CI 1.03–1.08], $P < .001$), COPD (OR 3.03 [95%CI 1.01–9.10], $P = .048$) and renal insufficiency (OR 14.44 [95%CI 1.88–110.64], $P = .010$) were identified as independent predictors of in-hospital death. Notably, a more recent implantation year was related to better in-hospital survival (in-hospital mortality: OR 0.73 [95%CI 0.57–0.93], $P = .010$). Furthermore, elevated BNP (OR 8.57 [95%CI 1.09–67.47], $P = .041$) and hsTnI-levels (OR 5.59 [95%CI 1.54–20.28],

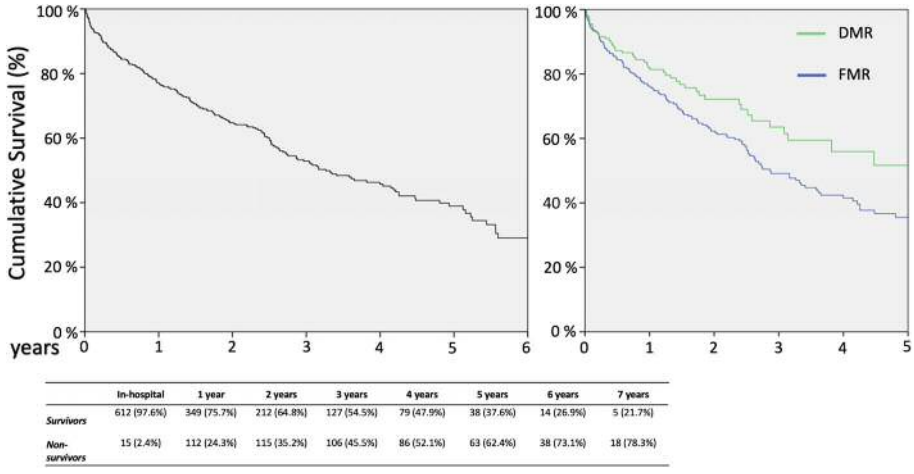

FIGURE 3 Long-term survival course of the patients treated with MitraClip implantation overall and stratified for etiology. Long-term survival of the study population after successful edge-to-edge repair (for details, see text)

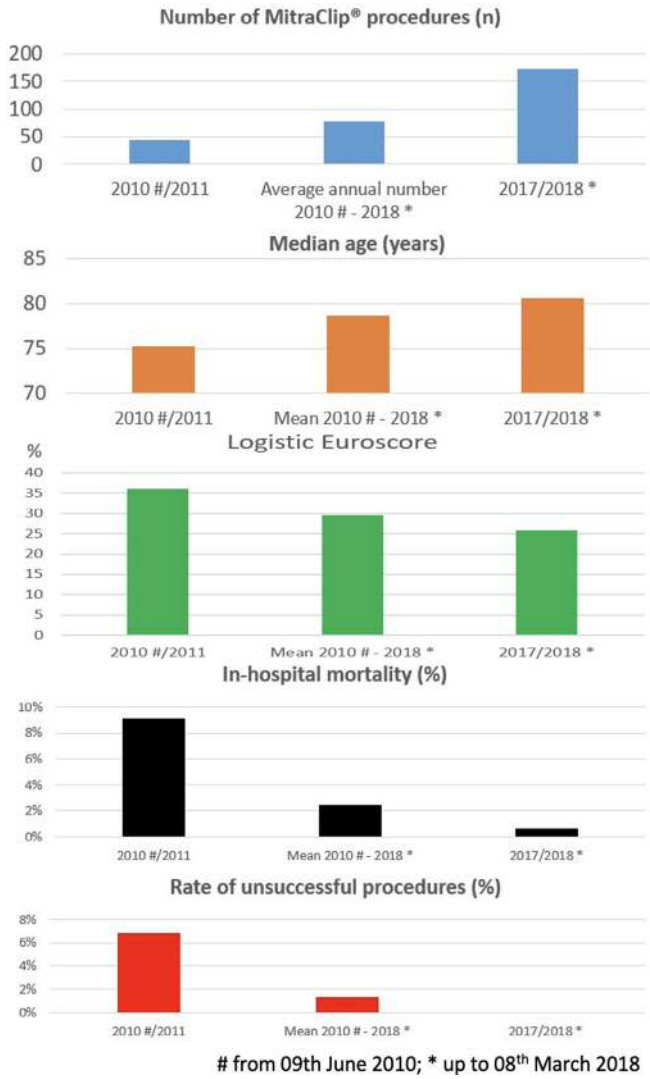

FIGURE 4 Comparison of implantation numbers, median age, mean logistic Euroscore, in-hospital mortality and implantation success. Comparison of implantation numbers, median age, mean logistic Euroscore, in-hospital mortality and implantation success between the first and the most recent implantation year included in this analysis. Going along with a marked increase in implantation numbers, in-hospital mortality and the rate of unsuccessful procedures decreased consequently over the years despite an older age at the index procedure, which can only partially be explained by a trend to a lower risk profile

P = .009) at baseline were predictive of higher in-hospital mortality (Figure 5 and Table 2).

3.5 | Baseline predictors of 1-year mortality

As expected, patients' age > 80 years was associated with an increased 1-year mortality (HR 1.70 [95%CI 1.17–2.46], P = .005). Renal insufficiency (HR 2.21 [95%CI 1.38–3.55], P < .001), a higher logistic Euroscore (HR 1.03 [95%CI 1.02–1.04], P < .001), a higher grade of tricuspid regurgitation (HR 1.30 [95%CI 1.04–1.64], P = .021) as well as right ventricular dysfunction (HR 1.75 [1.17–2.61], P = .007) before the index procedure were all predictive of a higher 1-year mortality. COPD (univariate HR 1.67 [95%CI 1.06–2.62], P = .026; multivariate HR 1.62 [95% CI 0.97–2.71], P = .064), coronary artery disease (univariate HR 2.11 [95%CI 1.34–3.31], multivariate HR 1.56 [95%CI 0.88–2.75], P = .001) and a history of myocardial infarction (univariate HR 1.88 [95%CI 1.28–2.75, P = .001], multivariate HR 1.33 [95%CI 0.81–2.17-2.91], P = .255) were also found to be associated with increased 1-year mortality(Figure 5 and Table 3).

Remarkably, elevated levels of creatinine, BNP and hsTnI were all accompanied by elevated 1-year mortality. Both hsTnI-level ≥ 24 pg/mL as well as BNP-level > 500 pg/mL were connected with a HR higher than 2.5 to die within the first year after edge-to-edge therapy. In contrast to in-hospital mortality, a later year of implantation could not be correlated to differences in the 1-year survival (HR 1.05 [95% CI 0.94–1.17], P = .397).

3.6 | In-hospital adverse events and impact on survival

Major adverse events during the index visit were recorded in 12 subjects (2.6%): 5 (1.1%) patients encountered acute kidney injury; two patients (0.4%) were transferred for surgical treatment due to either iatrogenic lesion of a leaflet or partial detachment of the device. Myocardial infarction was recorded in one (0.2%), pulmonary embolism in one (0.2%), stroke in two (0.4%) and hemodynamically relevant pericardial effusion in one (0.2%) case(s). Of all major adverse events, only the group of patients developing acute kidney injury (3.6% vs 0.3%) were over-represented in non-survivors of the first year.

3.7 | Differences between DMR and FMR

Patients with DMR were in median 3 years older (81.5 (76.3/85.9) vs 78.3 (73.9/82.5) years, P < .001) than patients with FMR at the time of procedure. Yet, patients with DMR had a lower risk profile as estimated by logistic Euroscore in comparison to FMR patients (22.3% [14.0/30.8] vs 28.1% [19.9/40.4], P < .001). Regarding the 1-year (DMR: 79.5% vs FMR: 74.9%, P = .304) and the 5-year survival (DMR: 44.4% vs FMR: 36.4%, P = .531), no significant differences were observed between both groups. Nevertheless, the Cox regression analysis for long-term mortality demonstrated a higher survival rate of DMR patients in comparison to FMR patients (crude HR 0.66 [95%CI 0.48–0.91], P = .012) (Figure 1).

4 | DISCUSSION

TVMR by edge-to-edge therapy is a frequently used therapeutic option for patients with symptomatic FMR and DMR—if anatomically suitable—in patients deemed to be at elevated surgical risk.[15]

TABLE 1 Baseline characteristics of all patients included in the retrospective analysis stratified for survival status at 1-year follow-up

Parameter	Survivors (n = 349; 75.7%)	Non-survivors (n = 112; 24.3%)	*P*-value
Age at procedure (years)	78.2 (73.6/83.1)	80.4 (74.4/84.7)	.068
Age > 70 years	298 (85.4%)	99 (88.4%)	.423
Female gender	154 (44.1%)	52 (46.4%)	.670
Height (cm)	169 (163/175)	167 (160/174)	.034
Weight (kg)	74.0 (65.0/84.0)	71 (63.5/80.0)	.218
BMI (kg/m^2)	25.7 (23.4/27.8)	25.2 (23.0/27.8)	.655
In-hospital stay (days) after procedure	5 (4/6)	6 (5/8)	<.001
NYHA III or IV	284 (86.6%)	95 (95.0%)	.021
Cardiovascular risk factors			
Obesity	50 (14.5%)	17 (15.6%)	.786
Art. hypertension	286 (81.9%)	96 (85.7%)	.357
Diabetes mellitus	96 (27.5%)	34 (30.4%)	.560
Intervention parameters			
FMR	200 (57.3%)	67 (59.8%)	.639
DMR	105 (30.1%)	27 (24.1%)	.223
Mixed etiology	44 (12.6%)	18 (16.1%)	.356
Number of implanted clips	1 (1/2)	1 (1/2)	.572
Logistic Euroscore I (points)	24.0 (17.7/34.7)	37.0 (24.5/51.2)	<.001
Comorbidities			
COPD	45 (12.9%)	24 (21.4%)	.028
PAH	215 (61.8%)	72 (64.3%)	.634
Atrial fibrillation	247 (70.8%)	78 (69.6%)	.819
Renal insuffiency	150 (43.1%)	76 (67.9%)	<.001
CAD	212 (60.9%)	88 (78.6%)	.001
History of myocardial infarction	80 (22.9%)	43 (38.4%)	.001
PAD	32 (9.2%)	14 (12.5%)	.306
History of stroke	37 (10.6%	13 (11.6%)	.766
History of cardiac surgery	69 (19.8%)	32 (28.6%)	.050
History of aortic valve replacement	11 (9.8%)	22 (6.3%)	.300
History of surgical MVR/r	2 (1.8%)	6 (1.7%)	.963
Pacemaker	112 (32.1%)	34 (30.4%)	.731
Implantable cardioverter-defibrillator	64 (18.3%)	21 (18.8%)	.922
Medication			
Diuretics	317 (90.8%)	105 (94.6%)	.210
RAS-blockers	295 (84.5%)	94 (84.7%)	.968
Betablockers	286 (81.9%)	90 (81.1%)	.837
Echocardiography			
LVEF (%) pre	40.0 (30.0/55.0)	35.0 (27.5/50.0)	.025
MR (grade)[a] pre-procedure	0:0.0%; I:0.0%; II:7.4%; III:92.6%	0:0.0%, I:0.0%, II:6.3%, III:93.8%	.669
MR (grade)[a] at discharge	0:6.7%, I:66.0%, II:23.5%, III:3.8%	0:5.9%; I:60.8%, II:29.4%, III:3.9%	.275
TR (rate) pre-procedure	0:6.9%, I:38.2%; II:36.0%; III18.9%	0:3.8%; I:31.1%, II:36.8%, III:28.3%	.022
P_{mean} MV (mmHg) pre-procedure	2.0 (1.1/3.0)	3.0 (2.0/4.0)	.249
RV dysfunction pre-procedure	84 (38.4%)	2 (40.0%)	.940
sPAP (mmHg) pre-procedure	50.0 (45.0/60.0)	53.0 (45.0/60.0)	.585
TAPSE (cm) pre-procedure	1.7 (1.4/2.1)	1.6 (1.3/2.2)	.320

(Continues)

TABLE 1 (Continued)

Parameter	Survivors (n = 349; 75.7%)	Non-survivors (n = 112; 24.3%)	*P*-value
Laboratory examinations			
Creatinine (mg/dL) pre-procedure	1.18 (0.93/1.61)	1.69 (1.08/2.11)	<.001
BNP (pg/mL) pre-procedure	488.0 (236.0/1080.0)	933.5 (540.8/2161.8)	<.001
hsTnI (pg/mL) pre-procedure	14.9 (5.8/37.2)	37.3 (17.2/65.9)	<.001
Exercise testing			
6 min walk-test (m/6 min)	281.5 (220.0/396.3)	220.0 (46.3/282.5)	.078

Bold values indicate *p*-values <.05.

Abbreviations: BMI, body mass index; NYHA, New York Heart Association; FMR, functional mitral valve regurgitation; DMR, degenerative mitral valve regurgitation; COPD, chronic obstructive pulmonary disease; PAH, pulmonary artery hypertension; CAD, coronary artery disease; PAD, peripheral artery disease; MVR/r, mitral valve repair or replacement ; RAS, renin-angiotensin; LVEF, left ventricular ejection fraction; MR, mitral valve regurgitation; TR, tricuspid valve regurgitation; P_{mean}, mean pressure; MV, mitral valve; RV, right ventricular; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; BNP, brain natriuretic peptide; hsTnI, high sensitive Troponin I.

[a]Classified in four grades: 0, no/trace, I, mild, II, moderate, III, severe.

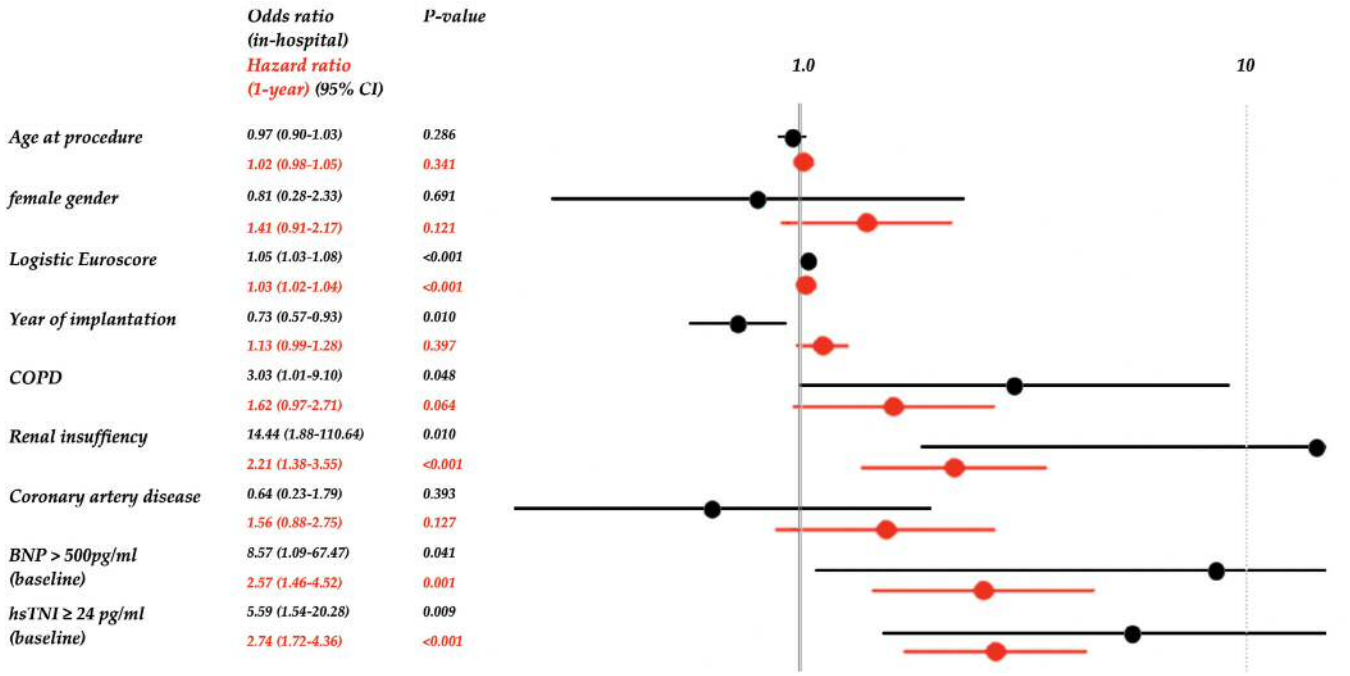

FIGURE 5 Predictors for in-hospital and 1-year mortality. Forrest plot illustrating logistic regressions (odds/hazard ratios, 95% CI in brackets, multivariate analysis) for factors with impact on in-hospital and 1-year mortality. For details, see text and Tables 2 and 3

The key findings of the present study may be summarized as follows:

1 In a large monocentric cohort of 627 patients treated with TMVR by edge-to-edge therapy of substantially elevated surgical risk (mean logistic Euroscore 29.7%) with nearly complete long-term follow-up up to 7 years, documented mortality rates were as follows: in-hospital 2.4%, mortality after 1 year 24.3%, after 3 years 45.5%, after 5 years 62.4% and after 7 years 78.3%.
2 The technical success rate was high (98.7%) and the rate of major in-hospital adverse events was low (2.6%).
3 Regarding baseline characteristics, patients' comorbidities (COPD, renal insufficiency), a higher logistic Euroscore and elevated baseline levels of biomarkers (Creatinine, BNP, hsTNI) were all associated with elevated in-hospital and 1-year mortality.
4 Right-ventricular dysfunction and a higher grade of tricuspid regurgitation were found to be predictive for lower 1-year survival.
5 A later implantation year reduced in-hospital mortality, but without having significant influence on 1-year survival. In-hospital mortality decreased substantially over the years despite a higher percentage of patients elder than 70 years.

TABLE 2 Predictors of in-hospital death in patients treated with MitraClip implantation (multi-variate regression model was adjusted for age)

	Univariate		Multivariate	
Parameter	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Age at procedure (years)	0.97 (0.90–1.03)	.286		
Age > 70 years	0.36 (0.11–1.15)	.083		
Female gender	0.75 (0.26–2.12)	.581	0.81 (0.28–2.33)	.691
Cardiovascular risk factors				
Obesity	0.42 (0.06–3.26)	.409	0.38 (0.05–2.93)	.350
Art. hypertension	0.44 (0.14–1.43)	.172	0.49 (0.15–1.62)	.242
Diabetes mellitus	0.65 (0.18–2.31)	.501	0.61 (0.17–2.20)	.451
Intervention parameters				
Number of implanted clips	0.98 (0.42–2.25)	.955	1.00 (0.44–2.31)	.994
Logistic Euroscore	1.05 (1.03–1.08)	**<.001**		
Implantation year	0.72 (0.57–0.91)	**.005**	0.73 (0.57–0.93)	**.010**
Comorbidities				
COPD	3.14 (1.05–9.42)	**.041**	3.03 (1.01–9.10)	**.048**
PAH	0.89 (0.32–2.48)	.819	0.90 (0.32–2.51)	.839
Atrial fibrillation	1.56 (0.44–5.61)	.493	1.75 (0.48–6.40)	.400
Renal insuffiency	14.90 (1.95–114.00)	**.009**	14.44 (1.88–110.64)	**.010**
CAD	0.62 (0.22–1.72)	.356	0.64 (0.23–1.79)	.393
History of myocardial infarction	1.82 (0.64–5.20)	.262	1.74 (0.61–5.00)	.301
PAD	2.41 (1.05–11.04)	**.041**	3.22 (0.99–10.51)	.053
History of stroke	1.97 (0.54–7.15)	.304	1.95 (0.54–7.09)	.312
History of cardiac surgery	1.60 (0.54–4.74)	.400	1.49 (0.49–4.48)	.480
History of aortic valve replacement	1.91 (0.81–4.50)	.136	1.98 (0.83–4.73)	.123
Pacemaker	1.18 (0.40–3.51)	.764	1.16 (0.39–3.46)	.784
Implantable cardioverter-defibrillator	1.40 (0.39–5.04)	.611	1.22 (0.33–4.52)	.767
Echocardiography				
LVEF < 50%	4.88 (1.09–21.83)	**.038**	4.57 (0.99–21.06)	.051
LVEF < 30%	2.95 (1.02–8.46)	**.045**	2.68 (0.88–8.21)	.085
MR (grade) at discharge	1.01 (0.34–2.97)	.988	0.95 (0.31–2.86)	.925
TR (grade) pre-procedure	1.33 (0.74–2.38)	.347	1.42 (0.78–2.61)	.253
P_{mean} MV (mmHg) pre-procedure	0.54 (0.28–1.02)	.058	0.53 (0.27–1.05)	.071
RV dysfunction pre-procedure	2.00 (0.71–5.56)	.192	1.96 (0.70–5.49)	.202
sPAP (mmHg) pre-procedure	1.00 (0.95–1.06)	.869	1.01 (0.96–1.06)	.767
TAPSE (cm) pre-procedure	0.19 (0.01–3.31)	.253	0.17 (0.01–3.33)	.240
Laboratory examinations				
Creatinine >1.2 mg/dL pre-procedure	2.41 (0.76–7.66)	.135	2.40 (0.76–7.62)	.138
BNP > 500 pg/mL pre-procedure	8.59 (1.09–67.54)	**.041**	8.57 (1.09–67.47)	**.041**
hsTnI ≥ 24 pg/mL pre-procedure	5.56 (1.53–20.13)	**.009**	5.59 (1.54–20.28)	**.009**

Bold values indicate *p*-values <.05.

Abbreviations: BMI, body mass index; NYHA, New York Heart Association; FMR, functional mitral valve regurgitation; DMR, degenerative mitral valve regurgitation; COPD, chronic obstructive pulmonary disease; PAH, pulmonary artery hypertension; CAD, coronary artery disease; PAD, peripheral artery disease; MVR, mitral valve replacement; RAS, Renin-angiotensin; LVEF, left ventricular ejection fraction; MR, mitral valve regurgitation; TR, tricuspid valve regurgitation; P_{mean}, mean pressure; MV, mitral valve; RV, right ventricular; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; BNP, brain natriuretic peptide; hsTnI, high-sensitive Troponin I.

6 Regarding long-term prognosis, differences in etiology pointed to a better survival in DMR patients, while differences in mid-term follow-up after 1 and 5 years were not statistically significant

In 2015, the Mitral Valve Academic Research Consortium (MVARC) published consensus recommendations for endpoints of trials investigating outcomes of mitral valve disease.[11] With respect to

TABLE 3 Predictors of 1-year mortality in patients treated with MitraClip implantation (multi-variate Cox regression model was adjusted: for adjustment (I) age and sex; for adjustment (II) age, sex, NYHA class, LVEF, tricuspid valve regurgitation, coronary artery disease, previous myocardial infarction, chronic kidney disease, and COPD)

	Univariate		Multivariate (adjustment I)		Multivariate (adjustment II)	
Parameter	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
Age at procedure (years)	1.02 (0.99–1.05)	.173	1.02 (0.99–1.05)	.182	1.02 (0.98–1.05)	.341
Age > 70 years	1.25 (0.70–2.23)	.446	1.24 (0.69–2.23)	.466	1.21 (0.57–2.23)	.733
Female gender	1.06 (0.73–1.54)	.747	1.03 (0.71–1.49)	.886	1.41 (0.91–2.17)	.121
Etiology						
DMR	0.76 (0.50–1.18)	.222	0.67 (0.43–1.06)	.090	1.02 (0.58–1.79)	.944
Cardiovascular risk factors						
Obesity	1.10 (0.65–1.84)	.731	1.16 (0.69–1.97)	.573	1.12 (0.63–2.00)	.699
Art. hypertension	1.28 (0.75–2.17)	.361	1.21 (0.71–2.07)	.477	1.40 (0.75–2.60)	.293
Diabetes mellitus	1.12 (0.75–1.67)	.585	1.15 (0.77–1.72)	.504	0.77 (0.49–1.23)	.277
Intervention parameters						
Number of implanted clips	0.95 (0.70–1.29)	.740	0.94 (0.69–1.30)	.719	1.04 (0.74–1.46)	.820
Logistic Euroscore	1.03 (1.02–1.04)	**<.001**				
Implantation year	1.06 (0.96–1.18)	.271	1.05 (0.94–1.17)	.397	1.13 (0.99–1.28)	.062
Comorbidities						
COPD	1.67 (1.06–2.62)	**.026**	1.70 (1.08–2.67)	**.022**	1.62 (0.97–2.71)	.064
PAH	1.08 (0.73–1.59)	.701	1.06 (0.72–1.56)	.774	0.69 (0.44–1.06)	.091
Atrial fibrillation	0.97 (0.65–1.44)	.864	0.93 (0.62–1.39)	.714	0.88 (0.55–139)	.576
Renal insuffiency	2.51 (1.69–3.73)	**<.001**	2.59 (1.74–3.86)	**<.001**	2.21 (1.38–3,55)	**<.001**
CAD	2.11 (1.34–3.31)	**.001**	2.16 (1.36–3.43)	**.001**	1.56 (0.88–2.75)	.127
History of myocardial infarction	1.88 (1.28–2.75)	**.001**	1.98 (1.34–2.91)	**.001**	1.33 (0.81–2.17)	.255
PAD	1.37 (0.78–2.39)	.273	1.43 (0.81–2.50)	.218	0.93 (0.50–1.75)	.826
History of stroke	1.08 (0.61–1.93)	.777	1.09 (0.61–1.94)	.778	1.36 (0.73–2.52)	.332
History of cardiac surgery	1.38 (0.93–2.06)	.109	1.47 (0.98–2.20)	.064	0.80 (0.49.1.30)	.365
History of aortic valve replacement	1.24 (0.78–1.97)	.368	1.24 (0.78–1.97)	.361	0.90 (0.53–1.53)	.693
Pacemaker	0.93 (0.62–1.39)	.732	0.95 (0.63–1.43)	.795	0.81 (0.51–1.29)	.378
Implantable cardioverter-defibrillator	1.02 (0.63–1.64)	.940	1.11 (0.68–1.81)	.684	0.97 (0.54–1.74)	.906
Echocardiography						
LVEF < 50%	1.26 (0.84–1.90)	.259	1.42 (0.93–2.18)	.109	0.89 (0.55–1.46)	.654
LVEF < 30%	1.39 (0.90–2.15)	.143	1.56 (0.99–2.48)	.058	1.12 (0.67–1.87)	.670
MR (grade) at discharge	1.16 (0.86–1.55)	.339	1.17 (0.87–1.58)	.295	1.21 (0.85–1.72)	.291
TR (grade) pre-procedure	1.32 (1.06–1.66)	**.014**	1.30 (1.04–1.64)	**.021**	1.28 (1.01–1.63)	**.043**
P_{mean} MV (mmHg) pre-procedure	1.13 (0.89–1.43)	.324	1.14 (0.90–1.45)	.287	1.15 (0.88–1.51)	.294
RV dysfunction pre-procedure	1.74 (1.16–2.60)	**.007**	1.75 (1.17–2.61)	**.007**	1.38 (0.87–2.21)	.175
sPAP (mmHg) pre-procedure	1.00 (0.98–1.02)	.780	1.00 (0.98–1.02)	.803	0.99 (0.97–1.01)	.186
TAPSE (cm) pre-procedure	0.77 (0.43–1.36)	.361	0.76 (0.43–1.36)	.356	1.14 (0.58–2.22)	.707
Laboratory examinations						
Creatinine > 1.2 mg/dL pre-procedure	1.92 (1.30–2.84)	**.001**	1.98 (1.33–2.95)	**.001**	1.47 (0.93–2.32)	.097
BNP > 500 pg/mL pre-procedure	3.43 (2.14–5.50)	**<.001**	3.55 (2.21–5.71)	**<.001**	2.57 (1.46–4.52)	**.001**
hsTnI ≥ 24 pg/mL pre-procedure	3.31 (2.21–4.95)	**<.001**	3.36 (2.24–5.04)	**<.001**	2.74 (1.72–4.36)	**<.001**

Bold values indicate *p*-values <.05.

Note: Regarding multivariate regression model with adjustment II: Creatinine >1.2 mg/dL pre-procedure was not adjusted for renal insufficiency; age > 70 years was not adjusted for the continues variable age; LVEF < 50% and LVEF < 30% were not adjusted for the continues variable LVEF.

Abbreviations: BMI, body mass index; NYHA, New York Heart Association; FMR, functional mitral valve regurgitation; DMR, degenerative mitral valve regurgitation; COPD, chronic obstructive pulmonary disease; PAH, pulmonary artery hypertension; CAD, coronary artery disease; PAD, peripheral artery disease; MVR, mitral valve replacement; RAS, Renin-angiotensin; LVEF, left ventricular ejection fraction; MR, mitral valve regurgitation; TR, tricuspid valve regurgitation; P_{mean}, mean pressure; MV, mitral valve; RV, right ventricular; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; BNP, brain natriuretic peptide; hsTnI, high-sensitive Troponin I.

these recommendations, all-cause mortality is an objective endpoint without bias and should be preferred compared to cardiac mortality as primary endpoint.

Data on long-term survival after edge-to-edge therapy for MR are still limited. In this large monocentric retrospective analysis, we recorded a very high success rate, a rather low rate of adverse events and found a relatively low in-hospital mortality of 2.4%, whereas long-term mortality was moderate only. Regarding in-hospital and 1-year survival rate, these data are comparable with a trend to a slightly higher long-term mortality in comparison to other registry data. While first evidence on survival was grounded on a first feasibility trial (EVEREST-I[16]) and the prospectively randomized EVEREST-II study, reporting on MitraClip-therapy in selective subgroups with low perioperative risk and a relatively low mortality,[17,18] results of several multicenter registries were published over the last years. These demonstrated that the interventional therapy for MR has a significantly higher risk profile in these "real-world" cohorts (eg, TRAMI,[9,10] the European Sentinel Registry[19] and ACCESS-EU[20]) compared to the mentioned early trials.

The German transcatheter mitral valve interventions registry (TRAMI) is so far the largest European multicenter cohort of patients treated with edge-to-edge therapy for MR. In a prospectively enrolled subgroup, which comprised the data on 749 patients reported on a 30-day mortality of 4.5% and a 1-year mortality of 20.3%; the follow-up rate was 90.5%.[9] Besides periprocedural failure, NYHA-class IV, anemia, previous aortic valve intervention, impaired renal function, peripheral artery disease, severely reduced LVEF and severe tricuspid regurgitation were identified as most relevant predictors for 1-year mortality in this cohort. In a long-term follow-up of this database, mortality was estimated by 31.9% after 2 years and 53.1% after 4-years.[10] The Transcatheter Valve Treatment Sentinal Pilot Registry included 628 patients from 8 European countries; in-hospital mortality was comparable to our study (2.9%), whereas a relatively low 1-year mortality of 15.3% was reported.[19] The ACCESS-EU study included 567 patients at 14 European sites and reported a 1-year mortality of 18.2%.[20] The US TVT-registry included 2,952 patients treated in the United States and reported a 1-year mortality of 25.8%.[21] In an Italian registry (GRASP-IT, 304 patients), 1-year mortality was only 15.1%, 5-year mortality 47.3%.[22]

In comparison to the European registry data, our cohort was older (78.6 ± 7.3 years vs 75.3 ± 8.6 TRAMI; 74.3 ± 9.7 Sentinel; 73.7 ± 9.6 ACCESS-EU; 70 ± 10 GRASP-IT; but: 82 [74/86] years in US-TVT), and had a significantly higher logistic Euroscore (29.7 ± 16.9% vs 23.7 ± 16.0% TRAMI; 20.3 ± 16.7 Sentinel; 23.0 ± 18.3% ACCESS-EU), which might per se account for moderately diminished short- and long-term survival rates in our study. Furthermore, our cohort was almost balanced regarding sex (47.0% females vs 39.3% TRAMI; 36.9% Sentinel; 36.2% ACCESS-EU; 44.2% US-TVT; 36.2% GRASP-IT) and distribution of FMR as main cause for MR was lower compared to the mentioned other registry studies (57.4% vs 69.3% TRAMI; 72.0% Sentinel; 69.3 ACCESS-EU; 78.9% GRASP-IT; but: 8.6% in US-TVT).[9,10,19-22]

With the present studies we identified patient several comorbidities as most relevant predictors for in-hospital and 1-year mortality. As expected, a higher logistic Euroscore I and patients' age older than 80 years were risk factors for a lower 1-year survival. In our cohort, comorbidities of COPD, renal impairment and coronary artery disease including history of myocardial infarction at baseline were age-independent predictors for increased 1-year mortality. In analogy to TRAMI, the predictive value of a reduced LVEF regarding prognosis was not found to be of statistical significance.[23] On the other hand, reduced right-ventricular function and higher rates of tricuspid regurgitation at baseline could be associated with lower one-year survival. Tricuspid regurgitation severity is positively influenced by edge-to-edge therapy for MR—especially in patients with significantly elevated systolic pulmonary pressure.[24] Higher grades of tricuspid regurgitation[10] and of systolic pulmonary pressure[25] before treatment were also reported to be prognosis-relevant in the TRAMI-population. In the TRAMI-cohort, procedural failure was the factor most strongly associated with increased 1-year mortality. As periprocedural failure was minimal (1.3%) in our cohort (in comparison to TRAMI with 3.2%[9]), we decided to exclude these patients and to report only results of treated patients as mentioned in the result section. Regarding the impact of major in-hospital adverse events on survival, it was not surprising to find an association between kidney failure as well as periprocedural pulmonary embolism with decreased survival in our cohort, although conclusions should be drawn carefully due to the very small numbers of events.

One of the most important findings of our study is that the later the year of implantation (linked with more implantation experience), we observed a striking reduction of in-hospital mortality (Figure 4), although this effect was already neutralized at 1-year follow-up. We suggest that a lower risk profile of patients despite higher age might partially account for this finding (see also Figure S1). Considering the analyzed implantation period of more than 7.5 years, the overall mean in-hospital mortality was 2.40%, which is comparable to the findings in the ACCESS-EU (2.0%[20]), Sentinel (2.9%[19]), and TRAMI-cohorts (2.4%[9]). The last inclusion year of our present study (2017/18), was characterized by an in-hospital mortality as low as 0.6%—which is even lower compared to the mortality established in a global study using the latest generation of the MitraClip device (EXPAND-Study on MitraClipNTR/XTR; in-hospital mortality 0.9% [presented at ESC 2019]). The largest real-word database on the in-hospital safety-outcomes including 13,575 patients undergoing edge-to-edge repair in Germany 2011 and 2015 demonstrated annual in-hospital mortality rates of 3.1% to 3.6% and found no significant differences over the years of treatment.[6] Of course, these were pooled data derived from all nationwide hospital sites. Thus, the results from our study demonstrate improvements in short-term survival over the years, which might be in part attributed to the increasing experience of the interventionalists, optimal patient selection as well as improvements in technical aspects of the procedure. Interestingly, the survival at 1-year was not modified by improved in-hospital mortality, which might further support the concept, that long-term survival is mainly determined by patients' comorbidities. In analogy to other published registry

data,[10,26] we did not find a statistically significant impact of etiology regarding mid-term survival; nevertheless, DMR patients had a better long-term survival and an observed difference as well as a lower hazard ratio for DMR-patients might partially be explained by a lower risk profile as determined by logistic Euroscore despite higher mean age.

4.1 | Limitations

The current study has some limitations. Firstly, the design is a monocentric retrospective analysis on an all-comer population of patients after interventional edge-to-edge repair for MR without any control group. According to MVARC-recommendations and due to the study design, all-cause mortality was defined as primary endpoint without further substratification. Importantly, follow-up rate was almost complete (96.7%) excluding selection bias widely. Secondly, in-hospital major adverse events were rare due to a high safety of the procedure on the one hand; yet, conclusions on potential impact on prognosis have to be interpreted with caution, mainly because of the small number of events.

5 | CONCLUSION

In this large monocentric "real-world" cohort of patients undergoing edge-to-edge repair for MR with long-term follow-up, we could demonstrate very low rates of periprocedural failure (1.3%) and in-hospital major adverse events (2.6%). In the present real-world cohort, patients were older and had a higher logistic Euroscore compared to published registry data. We provide further evidence, that prognosis after edge-to-edge repair is substantially influenced by comorbidities. Importantly, we could document a reduction of short-term mortality after TMVR which goes parallel with the increasing treatment volume of the interventionalists. Our results might allow optimization of patient selection for this beneficial and widely safe treatment.

ACKNOWLEDGEMENTS

This work contains results that are part of the doctoral thesis of Kevin Bachmann and Sonja Born. Thomas Münzel is PI of the DZHK (German Center for Cardiovascular Research), Partner Site Rhine-Main, Mainz, Germany.

CONFLICTS OF INTEREST

F. K.: consultancy and lecture honoraria from Abbott, Cardiac Implants, Edwards Lifesciences. L. H.: lecture honoraria from MSD. A. B. -F: lecture honoraria from Edwards and consultancy from Abbott and NeoChord. E. S.: lecture honoraria from Edwards Lifesciences and Medtronic. R. S. v. B: consultancy and lecture honoraria from Abbott Structural Heart, Boehringer Ingelheim, Cardiac Dimensions, Edwards Lifesciences, GE Health Systems and Philips Healthcare. All other authors state that there is no conflict of interest.

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SUPPORTING INFORMATION

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

How to cite this article: Geyer M, Keller K, Born S, et al. Predictors of short- and long-term outcomes of patients undergoing transcatheter mitral valve edge-to-edge repair. *Catheter Cardiovasc Interv*. 2021;97:E390–E401. https://doi.org/10.1002/ccd.29068