Original Studies

Long-Term Survival and Preprocedural Predictors of Mortality in High Surgical Risk Patients Undergoing Percutaneous Mitral Valve Repair

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Objectives: To evaluate long-term survival in high surgical risk patients undergoing percutaneous mitral valve repair (MVR) using the MitraClip® system and to identify preprocedural predictors of long-term mortality. Background: Data for long-term survival and preprocedural predictors of mortality after percutaneous MVR in high surgical risk patients are sporadic. Methods: From January 2009 to April 2013, 136 consecutive high surgical risk patients, with symptomatic moderate-to-severe or severe mitral regurgitation (MR), underwent percutaneous MVR using the MitraClip system. Cardiac and overall survival was determined at one and 2 years postprocedure. Univariate and multivariate analysis was performed to identify preprocedural predictors of long-term mortality. Results: One year postprocedure, cardiac and overall survival was 86.7% and 84.6%, respectively and at 2 years cardiac and overall survival was 77.7% and 74.8%, respectively. In univariate analysis advanced age, lower body mass index, impaired renal function, elevated levels of log-N-terminal-pro-brain-natriuretic-peptide (log-NTproBNP), poor performance in functional tests (New York Heart Association (NYHA) class) and high logistic Euroscore (LES) and Society of Thoracic Surgeons (STS) score were identified as preprocedural predictors of long-term cardiac mortality. In multivariate analysis preoperative NYHA class III and IV, elevated levels of log-NTproBNP and advanced age predicted long-term cardiac mortality. Conclusions: Percutaneous MVR using the MitraClip system has favorable long-term survival rates in high surgical risk patients. Preprocedural NYHA functional class III and IV, elevated log-NTproBNP levels and advanced age predict higher long-term cardiac mortality and should be considered during patient selection. © 2015 Wiley Periodicals, Inc.

Key words: mitral valve disease-edge to edge repair

INTRODUCTION

Mitral regurgitation (MR) is the second most common type of valvular heart disease requiring surgery in Europe [1]. Although the incidence of rheumatic heart disease has been reduced, MR is a growing public health problem because of population ageing [2]. Without surgical treatment, patients with symptomatic MR have reduced survival despite optimal medical therapy [3].

When feasible, surgical valve repair is the treatment of choice in patients with severe MR [4]. However, many patients in daily clinical practice are considered inoperable due to high periprocedural and postprocedural risk [5]. In these patients, percutaneous techniques

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may be an alternative therapy [4]. The best established technique to date is the transcatheter edge-to-edge mitral valve repair (MVR) using the MitraClip® system (Abbott Vascular, Santa Clara, CA) [6–9]. Mimicking the surgical procedure introduced by Ottavio Alfieri, the MitraClip system creates a double mitral valve (MV) orifice by positioning a clip which grasps the mid portions of the two leaflets [10]. According to the latest guidelines on valvular heart disease of the European Society of Cardiology (ESC), percutaneous edge-to-edge procedure may be considered in patients with symptomatic severe MR who fulfil the echocardiographic criteria of eligibility, are judged inoperable or at high surgical risk by a "heart team" and have a life expectancy greater than one year (recommendation class IIb, level of evidence C) [4]. Previously published data have proved MitraClip system's feasibility and efficacy in high risk patients [6,9,11,12]. The present study was designed to evaluate long-term survival in a consecutive cohort of high surgical risk patients undergoing percutaneous MVR using the MitraClip system in our center and to identify preprocedural predictors of long-term cardiac mortality.

MATERIALS AND METHODS

Study Population

All patients included in the study were fully informed about the procedure and signed a written consent form. The ethics committee of our institution approved the study protocol (R&D/Z-13.15/MitraClip®) and the latter was performed according to the principles outlined in the Declaration of Helsinki. Patients eligibility for treatment with transcatheter MVR according to current guidelines [4] was judged by an interdisciplinary "heart team," consisting at least of one cardiologist and cardiac surgeon.

Between January 2009 and April 2013, 136 consecutive patients underwent transcatheter MVR and were included in the study. All patients enrolled suffered from symptomatic moderate-to-severe or severe (grade 3+ or 4+) MR with or without LV dysfunction (ejection fraction <60%) or LV dilation (left ventricular end-systolic diameter >45 mm), and consequently had an indication for intervention according to the ESC guidelines [4]. They also exhibited high surgical risk based on the European System for Cardiac Operative Risk Evaluation (EuroSCORE) [13] or the Society of Thoracic Surgeons (STS) [14] mortality risk calculation (a logistic EuroSCORE (LES) >20% or an STS score >12% was considered "high risk") or were judged inoperable (despite lower thresholds of LES and STS score) due to a combination of additional factors associated with increased mortality as determined by the "heart team" (LVEF <30%, age >80 years, previous cardiac surgery, body mass index >35 or <18 kg/m^2, pulmonary hypertension, renal insufficiency, previous chest radiation, COPD and emphysema, porcelain aorta and frailty). Patients with evidence of an intracardiac mass, thrombus, or vegetation, active endocarditis, concomitant aortic valve pathology and unsuitable MV leaflet anatomy were excluded.

All study participants underwent preoperative evaluation following a standardized protocol that included a detailed medical history, physical examination, performance indices (Minnesota questionnaire, 6-min walk test (6MWT), New York Heart Association (NYHA) functional class), electrocardiography, transthoracic and transoesophageal echocardiography, and laboratory measurements. All patients were on optimal medical management according to current guidelines.

Individual patient charts were evaluated for clinical characteristics, including patient demographics, risk factors and operative data. Follow-up visits were scheduled in district hospitals one month after the procedure and consisted of physical examination, performance indices (Minnesota questionnaires, NYHA class) and transthoracic echocardiography. Follow-up survival information was evaluated by consulting the government death registries, via social security number. Cause of death was determined by contacting the referring physician or general practitioner. Long-term survival was defined as freedom from death (cardiac and noncardiac) at 1 and 2 years postprocedure. No patient was lost during follow-up regarding survival information.

Procedural Technique

Transcatheter MVR was performed by means of the MitraClip system, as previously described [15,16]. In brief, the MitraClip device system uses a guide catheter, a clip delivery catheter, and an implantable clip. The clip system is delivered to the left atrium via a transeptal puncture, advanced into the left ventricle, and then pulled back during systole, to grasp the MV leaflets. This results in permanent leaflet approximation and creation of a double orifice. The clip is a 4-mm-wide cobalt-chromium implant with two arms. On the inner portion of the clip arms there are small "grippers" to secure the leaflets when the clip arms are closed. In order to position the clip device correctly over the mitral orifice, it should be placed perpendicular to the line of leaflet coaptation and above the origin of the MR jet. These factors are mandatory to prevent clip disengagement and to obtain an acceptable MR reduction. A second or third clip was placed at operator discretion to obtain additional MR reduction. The procedure was performed under general anesthesia, using fluoroscopic and transoesophageal two- and three-dimensional echocardiographic guidance [16,17].

TABLE I. Baseline Characteristics

	$n = 136$
Patient related factors	
Age (yr)	74.5 ± 9.4
Female sex	44 (32.4)
Body mass index, (kg/m^2)	25.9 ± 4.7
Risk scores (%)	
LES	23.1 ± 15.7
ES II	9.6 ± 7.7
STS score	13.2 ± 8.2
Comorbidities	
Diabetes mellitus	31 (22.8)
Hypertension	70 (51.5)
Atrial fibrillation	72 (52.9)
COPD	28 (20.6)
Impaired renal function (GFR <45 ml/min/1.73 m^2)	54 (39.7)
Coronary artery disease	86 (63.2)
Previous CABG	58 (42.6)
Stroke/transient ischemic attack	20 (14.7)
Performance	
NYHA III or IV	122 (89.7)
6-MWT distance, (m)	273 ± 120
NTproBNP, (pg/ml)	4591 ± 6178
Cardiac related factors	
LVEF (%)	36.4 ± 15.3
Mitral regurgitation-etiology	
Degenerative	23 (16.9)
Functional	106 (77.9)
Mixed	7 (5.1)
Pulmonary hypertension*	
Moderate (sPAP = 31–55 mm Hg)	96 (70.6)
Severe (sPAP >55 mm Hg)	25 (18.4)
CRT	30 (22.1)

Values are *n* (%) or mean ± SD.

CABG: Coronary Artery Bypass Graft; COPD: Chronic Obstructive Pulmonary Disease; CRT: Cardiac resynchronization therapy; ESII: Euroscore II; GFR: Glomerular filtration rate; LES: Logistic Euroscore; LVEF: Left Ventricle Ejection Fraction; NTproBNP: N-terminal-pro-brain-natriuretic-peptide; NYHA: New York Heart Association; sPAP: systolic pulmonary artery pressure; STS: Society of Thoracic Surgeons Risk Score; 6MWT: 6-Minute Walk Test; *Pulmonary hypertension defined by echocardiography as moderate (sPAP = 31–55 mm Hg) or severe (sPAP > 55 mm Hg).

Postprocedural Care

Management of antithrombotic therapy consisted of clopidogrel monotherapy, 75 mg once daily, for 1 month following the procedure without a loading dose. Patients receiving vitamin K antagonists before clip placement continued after the intervention along with the aforementioned clopidogrel regimen.

Statistical Analysis

Descriptive statistics were used to report patient characteristics. Continuous variables were reported as means and standard deviations (SD). Frequencies and percentages were used to report nominal variables. Univariate Cox proportional hazards regression analysis was performed to identify preprocedural predictors of long-term cardiac mortality. The measure of effect was the hazard ratio form the Cox model, with 95% confidence interval and P value. A two-sided P value of <0.05 was considered significant. Baseline variables that showed a univariate association with $P < 0.10$ with outcome were entered into the multivariate Cox proportional hazards regression analysis. For right censored-data (i.e. time to event), the Kaplan-Meier method was used to compute the long-term survival. All statistical analyses were performed using SPSS software (SPSS version 21.0 for Windows, IBM, Armonk, NY).

RESULTS

Baseline Characteristics

The full list of baseline characteristics is summarized in Table I. Transcatheter MVR was performed in 136 patients (mean age 74.5 ± 9.4 years, 92 males, 67.6%, Table I). The mean LES was $23.1 \pm 15.7\%$ (Table I); the mean STS score was $13.2 \pm 8.2\%$ (Table I). Most of the patients (63.2%) had a history of coronary artery disease while 42.6% had previous cardiac surgery. The majority suffered from functional MR (FMR) (106 patients, 77.9%); mean left ventricular ejection fraction (LVEF) was $36.4 \pm 15.3\%$ (Table I). At baseline, most of the patients were in NYHA functional class III or IV (122 patients, 89.7%). Severe pulmonary hypertension (defined by echocardiography as systolic pulmonary artery pressure >55mmHg) was noted in 18.4% of the patients (Table I).

Long-Term Survival

The 136 patients of the study population underwent a total of 143 procedures (Fig. 1a and b). Due to recurrent MR, seven patients had to undergo a redo procedure. Acute procedural success (APS), defined as a reduction of MR grade $\leq 2+$ by visual TEE quantification directly after clipping, was achieved in 132 of 143 procedures (92.3%). A second clip had to be used in 26 patients, while two patients received three clips. Thirty-day overall mortality was 3.5%, as five patients died, all due to cardiac causes (four end-stage heart failure and end cardiac arrest). During 2-years' follow-up, there were 35 deaths. The site-reported causes of death for these patients were: cardiac (82.9%, 29 of 35) and non-cardiac (17.1%, 6 of 35; 3 died of malignancy and 3 of pneumonia). In particular, 23 patients died due to decompensation of advanced heart failure, 3 patients died due to out of hospital cardiac arrest (ventricular fibrillation at presentation), 2 patients died due to sudden cardiac death, and 1 patient died due to myocardial infarction. Cardiac survival at one and 2 years

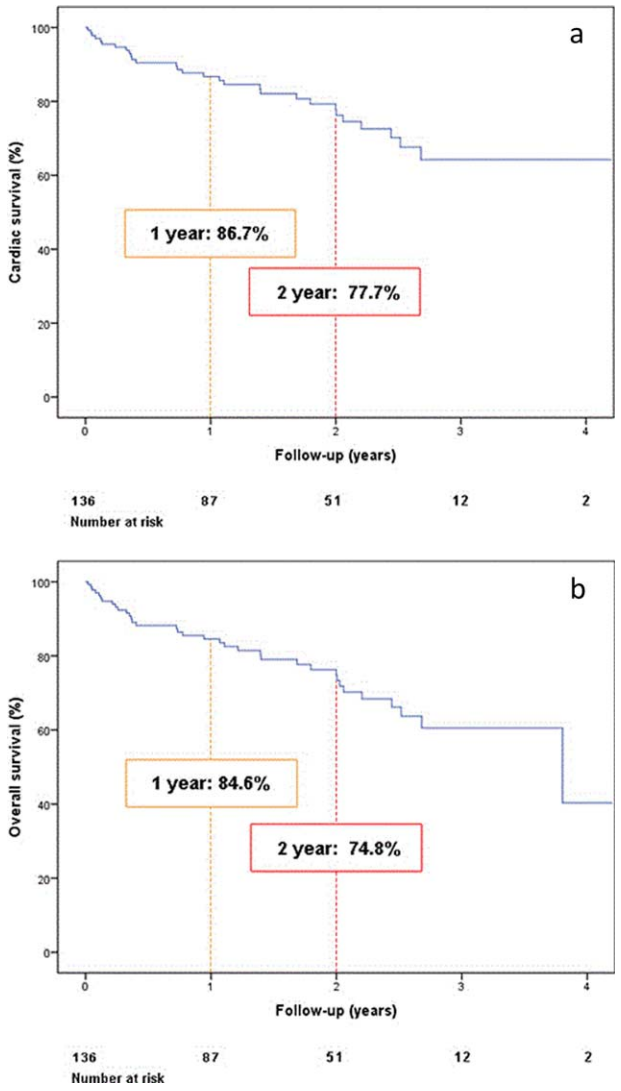

Fig. 1. (a) Cardiac survival at 1 and 2 years. Kaplan-Meier cardiac survival curves (%) at 1 and 2 years follow-up (136 patients treated by percutaneous MVR). (b) Overall survival at 1 and 2 years. Kaplan-Meier overall survival curves (%) at 1 and 2 years follow-up (136 patients treated by percutaneous MVR). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

postprocedure was 86.7% and 77.7%, respectively. Overall survival at one and 2 years postprocedure was 84.6% and 74.8%, respectively (Fig. 1a and b).

Periprocedural Predictors of Cardiac Mortality

Patients that did not achieve APS (No APS) had a higher cardiac death risk (OD 4.25, 95% CI 1.47–12.30, $P = 0.008$, Table II). MV gradient directly after clipping was >5 mm Hg in one patient. Additionally, 30 patients developed periprocedural complications. In particular, 8 patients had bleeding requiring transfusion (1 patient gastrointestinal bleeding, 7 patients access site bleeding), 6 patients had Mitraclip detachment/malposition, 3 patients had tamponade, 10 patients had acute decompensation of heart failure, 1 patient had transient ischemic attack, 1 patient had peripheral nerve palsy due to central line insertion and 1 patient had allergic shock due to protamine. Patients reporting complications were more likely to experience cardiac death (OD 5.31, 95% CI 2.14–13.18, $P < 0.01$, Table III). Thus, patients with no APS or with procedure related complications were at higher risk of cardiac death.

Preprocedural Predictors of Long-Term Cardiac Mortality

The preprocedural predictive value for long-term cardiac mortality of each of the baseline characteristics was assessed in univariate analysis. Advanced age (77.2 ± 7 years vs. 73.7 ± 9.9 years, Table IV), lower body mass index (BMI, 24.7 ± 4.6 kg/m^2 vs. 26.3 ± 4.8 kg/m^2, Table IV) and impaired kidney function (expressed as glomerular filtration rate (GFR) <45 ml/min, Table IV), were identified as preprocedural predictors of long-term cardiac mortality (HR 1.06, CI 95% 1.01–1.11, $P = 0.018$; HR 0.91, CI 95% 0.82–0.99, $P = 0.036$ and HR 2.93, CI 95% 1.38–6.22, $P = 0.005$, respectively, Table IV). The low preprocedural performance in NYHA (3.5 ± 0.6 vs. 3.0 ± 0.6, Table V) functional test was also related with long-

TABLE II. Acute Procedural Success

Acute procedural success	Cardiac death				
	Yes	No	Odds ratio	CI 95%	*P*
Acute success in 1 or 2 procedure	25 (86.2)	104 (97.2)	0.24	0.08–0.68	**0.008**
No APS	4 (13.8)	3 (2.8)	4.25	1.47–12.30	**0.008**
Redo procedure	6 (5.6)	1 (3.4)	0.58	0.08–4.23	0.59

Bold *P* values imply statistical significance.
CI: confidence interval; APS: acute procedural success.

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TABLE III. Periprocedural Complications

	Cardiac death				
	Yes	No	Odds ratio	CI 95%	*P*
Any complication	14/29 (48.3%)	16/107 (15.0%)	5.31	2.14–13.18	**<0.01**
Complication type					
Mitraclip detachment/malposition	1/14 (7.1%)	5/16 (31.2%)	0.33	0.02–5.05	0.4
Bleeding	3/14 (21.4%)	5/16 (31.2%)	NA	NA	NA
Tamponade	0/14 (0.0%)	3/16 (18.8%)	NA	NA	NA
Heart failure decompensation	10/14 (71.4%)	0/16 (0.0%)	NA	NA	NA
Neurologic event	0/14 (0.0%)	2/16 (12.5%)	NA	NA	NA
Allergic shock	0/14 (0.0%)	1/16 (6.2%)	NA	NA	NA

CI: confidence interval; NA: nonapplicable.
Bold *P* values imply statistical significance.

TABLE IV. Preprocedural Predictors of Long-Term Cardiac Mortality in Univariate Analysis

	Cardiac death				
	Yes	No	HR	CI 95%	*P*
Number	29	107			
Age (yr)	77.2 ± 7.0	73.7 ± 9.9	1.06	1.01-1.11	***0.018***
Female	7 (24.1)	37 (34.6)	0.67	0.28-1.53	0.333
Body mass index (kg/m^2)	24.7 ± 4.6	26.3 ± 4.8	0.91	0.82-0.99	***0.036***
Comorbidities					
Diabetes mellitus	6 (20.7)	25 (23.4)	1.03	0.41-2.53	0.95
Hypertension	13 (44.8)	57 (53.3)	0.70	0.33-1.45	0.34
Atrial Fibrillation	18 (62.1)	54 (50.5)	1.72	0.81-3.67	0.16
COPD	6 (20.7)	22 (20.6)	0.90	0.36-2.22	0.82
GFR <45 ml/min	18 (62.1)	36 (33.6)	2.93	1.38-6.22	***0.005***
Coronary artery disease	19 (65.5)	67 (62.6)	1.11	0.51-2.40	0.79
Previous CABG	14 (48.3)	44 (41.4)	1.15	0.55-2.38	0.71
Stroke/transient ischemic attack	3 (10.3)	17 (15.9)	0.66	0.20-2.16	0.49

CABG: Coronary Artery Bypass Graft; CI: confidence interval; COPD: Chronic Obstructive Pulmonary Disease; GFR: Glomerular filtration rate; HR: hazards ratio.
Bold *P* values imply statistical significance.

TABLE V. Preprocedural Predictors of Long-Term Cardiac Mortality in Univariate Analysis

	Cardiac death				
	Yes	No	HR	CI 95%	*P*
Performance					
NYHA	3.4 ± 0.6	3.0 ± 0.6	2.75	1.37-5.55	**0.005**
6-MWT distance (m)	241 ± 129	282 ± 117	1.00	0.99-1.00	**0.05**
Laboratory results					
Log-NTproBNP	8.3 ± 1.2	7.7 ± 1.2	1.55	1.11-2.16	**0.010**
Hemoglobin (mmol/Lt)	7.8 ± 1.0	7.9 ± 1.0	0.78	0.52-1.16	0.22
Creatinine (umol/Lt)	147 ± 56	128 ± 71	1.00	1.00-1.00	0.20
Cardiac related factors					
LVEF (%)	35.8 ± 16.1	36.6 ± 15.1	1.00	0.98-1.03	0.90
Mitral regurgitation-etiology					
Degenerative	4 (13.8)	19 (17.8)	Ref	Ref	0.48
Functional	23 (79.3)	83 (77.6)	0.98	0.34-2.82	0.96
Mixed	2 (6.9)	5 (4.7)	2.39	0.43-13.27	0.32
Pulmonary hypertension					
No	1 (3.5)	12 (13.1)	Ref	Ref	0.22
Moderate	21 (72.4)	75 (70.1)	2.90	0.39-21.56	0.30
Severe	7 (24.1)	18 (16.8)	5.11	0.63-41.7	0.13
CRT	4 (13.7)	26 (24.3)	0.48	0.17-1.38	0.17

CI: confidence interval; CRT: cardiac resynchronization therapy; HR: hazards ratio; log-NTproBNP: log-N-terminal-pro-brain-natriuretic-peptide; LVEF: Left Ventricle Ejection Fraction; NYHA: New York Heart Association; Ref: reference; 6-MWT: 6 Minute Walk Test.
Bold *P* values imply statistical significance.

TABLE VI. Preprocedural Predictors of Long-Term Cardiac Mortality in Univariate Analysis

	Cardiac death				
	Yes	No	HR	CI 95%	*P*
LES	30.8 ± 11.5	21.7 ± 14.7	1.02	1.00–1.04	***0.014***
ESII	11.5 ± 8.0	9.3 ± 7.7	1.03	0.99–1.07	0.21
STS	14.4 ± 7.9	13.2 ± 8.4	1.05	1.00–1.10	***0.035***
LES ≥ 20	22 (75.9)	47 (43.9)	3.30	1.41–7.75	***0.006***
ESII ≥ 5	23 (79.3)	69 (64.5)	2.00	0.81–4.91	0.13
ESII ≥ 10	14 (48.3)	38 (35.5)	1.47	0.71–3.05	0.30
STS ≥ 12	19 (65.5)	48 (44.9)	3.32	1.53–7.24	***0.003***

CI: confidence interval; ES: Euroscore; HR: hazards ratio; LES: logistic Euroscore; STS: Society of Thoracic Surgeons Risk Score.
Bold *P* values imply statistical significance.

TABLE VII. Preprocedural Predictors of Long-Term Cardiac Mortality in Multivariate Analysis

	Cardiac death				
	Yes	No	HR	CI 95%	*P*
Number	29	107			
Age (yrs)	77.2 ± 7.0	73.7 ± 9.9	1.07	1.02-1.13	**0.011**
NYHA	3.4 ± 0.6	3.0 ± 0.6	2.07	1.02-4.20	**0.045**
Log-NTproBNP	8.3 ± 1.2	7.7 ± 1.2	1.52	1.07-2.15	**0.018**

CI: confidence interval; HR: hazards ratio; log-NTproBNP: log-N-terminal-pro-brain-natriuretic-peptide; NYHA: New York Heart Association.
Bold *P* values imply statistical significance.

term cardiac mortality (HR 2.75, CI 95% 1.37–5.55, $P = 0.005$, Table V). Furthermore, derived from the laboratory data, higher preprocedural log-N-terminal-pro-brain-natriuretic-peptide (log-NTproBNP) levels (8.3 ± 1.2 vs. 7.7 ± 1.2, Table V) were associated with increased long-term cardiac mortality (HR 1.55; CI 95% 1.11-2.16, $P = 0.010$, Table V). Additionally, higher LES (30.8 ± 11.5 vs. 21.7 ± 14.7, Table VI) and STS score (14.4 ± 7.9 vs. 13.2 ± 8.4, Table VI) could predict long-term cardiac mortality (HR 1.02, CI 95% 1.00–1.04, $P = 0.014$ and HR 1.05, CI 95% 1.00–1.10, $P = 0.035$, respectively, Table VI), while a LES ≥20 and an STS score ≥12 constituted strong preprocedural predictors (HR 3.30, CI 95% 1.41–7.75, $P = 0.006$ and HR 3.32, CI 95% 1.53–7.24, $P = 0.003$, respectively, Table VI). Consequently, low GFR, advanced NYHA class, LES ≥20 and an STS score ≥12 formed the strongest preprocedural predictors of long term mortality in univariate analysis (Table IV–VI).

In multivariate analysis age, NYHA and log-NTproBNP were significantly associated with long-term cardiac mortality. In particular, advanced age, NYHA functional class III and IV and elevated levels of log-NTproBNP were associated with long-term cardiac mortality (HR 1.07, CI 95% 1.02–1.13, $P = 0.011$; HR 2.07, CI 95% 1.02–4.20, $P = 0.045$ and HR 1.52, CI 95% 1.07–2.15, $P = 0.018$, respectively, Table VII).

DISCUSSION

The present observational study was designed to investigate long-term survival in "real-world" high surgical risk patients undergoing percutaneous MVR using the MitraClip system and to identify preprocedural predictors of long-term cardiac mortality.

The profile of our cohort consisted of patients whose mean age was 74.5 years, had FMR (78%) and impaired left ventricle ejection fraction (mean LVEF was 36%). Moreover, they suffered from multiple comorbidities, including coronary artery disease (63%), atrial fibrillation (53%), and impaired renal function (40%). The majority of patients were highly symptomatic (90% were in NYHA functional class III or IV at baseline), a factor associated with worse outcomes [18,19]. Thus, patient's characteristics resemble those reported in ACCESS-EU registry and EVEREST II high-risk study [9,12]. These cornerstone studies, have reported the efficacy of MitraClip therapy in high-risk populations. In the ACCESS-EU population, mean age was 74 years, most patients had FMR (77%) and LVEF<40% (for more than half of the study population), presented with multiple comorbidities and the majority of patients were highly symptomatic (85% were in NYHA class III or IV) [9]. In the EVEREST II high-risk study, patients were older (mean age of 77 years), with multiple comorbidities, and suffered from symptomatic (90%

were in NYHA class III and IV) and predominantly functional MR (FMR 59%) [12].

In our study, mortality at 30 days was lower (3.5%) than the predicted surgical mortality for this patient cohort either using the mean LES (23.1%) or the mean STS score (13.2%), underlining the low risk of the procedure. At one year postprocedure, cardiac and overall survival was 86.7% and 84.6%, respectively. The latter demonstrated higher overall survival rates at one year after the procedure than that reported in ACCESS-EU registry and EVEREST II high-risk study (84.6% vs. 82% vs. 76%, respectively) [9,12]. The recently published European SENTINEL registry, which included patients with similar characteristics, reported similar one year survival rates (84.7% vs. 84.6%) [20]. At the second year postprocedure, cardiac and overall survival was 77.7% and 74.8%, respectively. Consequently, our data further expand the findings of the aforementioned studies and underscore that placement of the MitraClip device in high surgical risk patients, with functional MR and multiple comorbidities, is safe, feasible and accounts for favorable long-term survival rates.

Furthermore, we tried to elucidate possible preprocedural predictors of long-term cardiac mortality. LES and STS scoring models are surgical risk scores designed to estimate perioperative mortality (in-hospital or 30-day mortality) after surgical treatment [13,14,21]. Our data revealed that a LES $\geq$20 and an STS score $\geq$12 compose significant preprocedural predictors of long-term cardiac mortality for patients undergoing transcatheter MVR. Hence, the risk scores, even though overestimating periprocedural mortality risk, are useful in identifying high-risk surgical patients for transcatheter MV treatment and in predicting preprocedural long-term cardiac mortality.

In addition, previous studies have indicated that reduced forward stroke volume and renal dysfunction are independent preprocedural risk factors for long-term mortality in patients with primary MR [22], while high LES and STS score, elevated NTproBNP, advanced age and NYHA class IV predict 1-year mortality in patients with functional MR [22–24]. In our study, advanced age, lower BMI, impaired renal function, elevated levels of log-NTproBNP and poor performance in functional tests (NYHA class) were identified as preprocedural predictors of long-term cardiac mortality. In univariate analysis, low GFR and advanced NYHA class formed strong preprocedural predictors of long term mortality. Analysis with a multivariate model revealed that NYHA class III and IV, elevated levels of log-NTproBNP and advanced age were the strongest preoperative factors independently associated with long-term cardiac mortality.

Advanced heart failure is a clinical condition with poor prognosis that encompasses several features including dyspnea, NYHA class III, IV and elevated plasma NTproBNP levels [25]. Patients who remain symptomatic at rest or minimal exertion (NYHA III, NYHA IV) despite optimal medical and device treatment have a poor prognosis. Moreover, the failing myocardium releases NTproBNP and its high plasma levels correlate with heart failure severity and mortality [25]. Furthermore, older patients with heart failure frequently present with co-existing comorbidities leading in poor outcomes [26]. Therefore, older patients with advanced heart failure, as expressed by NYHA class III, IV and elevated log-NTproBNP levels, carry an adverse prognosis due to the physical course of the disease which is unlikely to be altered with MitraClip implantation. Patients who exhibit these characteristics reflect individuals with advanced heart failure where MitraClip implantation cannot reverse the clinical course of the disease and in such case, the intervention with MitraClip should be reconsidered. Thus, we suggest that log-NTproBNP levels, NYHA functional class and age represent preprocedural predictors of long-term cardiac mortality and should be considered during patient selection.

As far as the periprocedural data is concerned, we identified that patients with no APS and patients with procedure related complications were at higher risk of cardiac death. This finding, comes in accordance with results from previous studies [24].

Limitations of our study are its observational and nonrandomized character. Moreover, it is a single-centre trial, thus selection bias during the "heart team" evaluation process could be possible. The majority of the patients had to refer in their district hospitals for the follow-up visits, which caused compliance inconsistencies leading to inadequate data recruitment. Thus, we did not describe secondary end points such as quality of life scores, performance indices, residual MR grade, signs of reverse LV-remodeling and rehospitalization. Our main objective was to investigate the primary endpoint of long-term survival and to identify possible preprocedural predictors of long-term mortality. Finally, LES overestimates operative mortality, thus the novel predictive model Euroscore II could render a better risk stratification [27].

CONCLUSION

The results presented herein clearly demonstrate that MitraClip therapy in "real-world" high surgical risk patients, predominantly with functional MR and multiple comorbidities, is safe with favorable and sustained outcomes in terms of survival which extend to 2 years

after the procedure. In addition, advanced age, NYHA functional class III and IV and elevated levels of log-NTproBNP are strong preprocedural predictors of long-term cardiac mortality which advocate careful and restrictive selection of MitraClip candidates.

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