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Original Article

Prognosis for Mitral Valve Repair Surgery in Functional Mitral Regurgitation

Rafael Campos-Arjona,[1,2,3,4] Jorge Rodríguez-Capitán,[1,2,3,4] José D. Martínez-Carmona,[1,2,3,4] Alexey Lavreshin,[1,2,3,4] Loudes Fernández-Romero,[1,2,3,4] José M. Melero-Tejedor,[1,2,3,4] and Manuel Jiménez-Navarro[1,2,3,4]

Purpose: Our aim was to evaluate the development of new significant mitral regurgitation and long-term survival after mitral repair surgery in functional mitral regurgitation.
Methods: A retrospective observational analysis of the recurrence of functional mitral regurgitation (ischemic and nonischemic) and global mortality during follow-up of 176 patients who underwent mitral repair surgery between 1999 and 2018 in our center was conducted.
Results: The etiology of functional mitral regurgitation was ischemic in 55.7% of cases. After surgery, mitral regurgitation was 0-I in 92.3% of cases. We conducted a long-term clinical follow-up of a mean 42.2 months and an echocardiographic follow-up of a mean 41.8 months. We observed mitral regurgitation of at least grade II in 52 patients (36.9%). Survival at 1, 3, and 5 years was 78.8%, 66.7%, and 52.3%, respectively. Predictive factors for global mortality were age (hazard ratio = 1.038, p = 0.01) and a depressed preoperative ejection fraction. After a competing risk analysis, we found the only predictive factor for the recurrence of mitral regurgitation in our series to be age (sub-hazard ratio = 1.03, 95% confidence interval = 1.01–1.06, p = 0.016).
Conclusion: Repair surgery for functional mitral regurgitation shows age as the only independent predictor of recurrence. Age and depressed ejection fraction were predictors of mortality.

Keywords: mitral valve surgery, mitral valve repair, mitral regurgitation, functional mitral regurgitation, recurrent mitral regurgitation

[1]*Department of Heart and Cardiovascular Pathology, Virgen de la Victoria University Hospital, Malaga, Spain*
[2]*Department of Medicine and Dermatology, University of Malaga, Malaga, Spain*
[3]*Malaga Biomedical Research Institute (IBIMA), Malaga, Spain*
[4]*CIBERCV Cardiovascular Diseases. Carlos III Health Institute, Madrid, Spain*

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Corresponding author: Rafael Campos-Arjona. Department of Heart and Cardiovascular Pathology, Virgen de la Victoria University Hospital, Malaga, Spain
Email: rafaelcampos.car@gmail.com

Introduction

The presence of functional mitral regurgitation (MR) conditions a bad prognosis, with a progression that becomes even worse as the severity and symptoms of MR increase, and is associated with hospitalization for heart failure and higher long-term mortality.[1)]

Among patients with severe functional MR who remain symptomatic and have significant MR after optimization of medical treatment and resynchronization therapy (when this is indicated), surgery for the repair or replacement of the mitral valve is a therapeutic option, particularly for cases of an ischemic etiology with left ventricular ejection fraction (LVEF) >30%

who will undergo coronary artery bypass graft (indication I-C).[2–6)]

Despite performance of repair surgery on the mitral valve, different studies report considerable heterogeneity in the high recurrence rate of MR in follow-up (ranging from 20.3% and 27.6% at 5 and 10 years, respectively, in Petrus et al.[7)] to rates as high as 55%–70% at 10 years.[8)]) Moreover, no significant impact on long-term survival after surgery for mitral repair in functional MR has been established.[9–12)] Likewise, the majority of studies that assess the predictors of MR recurrence after repair and mortality offer discrepant results, and do not take mortality into account as a competing risk event.[7–13)]

For these reasons, a unanimous strategy for the surgical treatment of patients with functional MR has not yet been established,[8)] which is of particular importance given current developments in new transcatheter techniques for mitral valve repair/replacement.[5,8,14–16)]

The primary endpoint of our study was to evaluate the prognosis after surgery to repair functional MR at our center, with particular emphasis on the development of new significant MR and on long-term survival.

Materials and Methods

We conducted a retrospective observational study of functional MR (ischemic and nonischemic) patients undergoing surgical mitral repair at our center between 1999 and 2018.

Study population and surgical technique

We consecutively included all patients with functional or secondary MR for whom mitral repair surgery was indicated at our center between 1999 and 2018. The indication for surgical repair was established at medical–surgical sessions in which both clinical cardiologists and cardiac surgeons participated, bearing in mind the patient's preference. Echocardiographic classification of the type and grade of MR followed recommendations of the American Society of Echocardiography guidelines,[17)] which were classified as mild or grade I MR (effective regurgitant orifice area [EROA] <0.20 cm^2, regurgitant volume [RV] <30 ml, and regurgitant fraction [RF] <30%), moderate or grade II MR (EROA 0.20–0.29, RV 30–44 ml, and RF 30%–39%), grade III or moderate-to-severe MR (EROA 0.30–0.39, RV 45–59 ml, and RF 40%–49%), and severe or grade IV MR (EROA ≥0.40, RV ≥60 ml, and RF ≥50). Functional MR was defined as due to morphological or functional abnormalities of the left ventricle (whether ischemic or nonischemic dilated cardiomyopathy etiology) in which the main mechanism of MR is symmetric (due to ventricular dilation) or asymmetric (habitually of ischemic etiology) restriction of one or both mitral leaflets (Carpentier class IIIB). In all cases, restrictive annuloplasty was the surgical technique used to repair the mitral valve with the aim of reducing the anteroposterior diameter. The annuloplasty rings employed in most cases were ETlogix (asymmetric ring in the case of asymmetric restriction of a leaflet due to ischemic cause), Physio, or GeoForm (symmetric rings for cases with restriction of both leaflets in the context of ventricular dilation).

Variables analyzed and follow-up

Data were collected retrospectively from the heart surgery database and from the respective medical records of patients. Functional class was defined in accordance with the New York Heart Association (NYHA) functional classification, and the classification of LVEF was preserved (>55%), mildly depressed (45%–55%), moderately depressed (30%–45%), or severely depressed (<30%). Completeness of coronary arteries' revascularization has been defined as the successful treatment of all coronary lesions with a visually estimated diameter stenosis of ≥70% in vessels with a reference diameter ≥2 mm.

Concerning the short-term outcomes of surgery, we evaluated perioperative mortality (defined as death during hospital admission for mitral repair surgery or in the 30-day period after mitral repair), hospital stay, MR grade, and the LVEF after surgery. Patients who survived the perioperative period underwent long-term clinical and echocardiographic follow-up in which mortality, MR grade, LVEF, and functional class were evaluated.

Statistical analysis

Qualitative variables are expressed as a percentage, time variables as a mean and interquartile range, and all other continuous quantitative variables are expressed as a mean ± standard deviation. To identify predictor variables of mortality, a Cox model was used, calculating hazard ratio (HR) and the corresponding confidence interval (CI) at 95%. The statistical analysis of MR recurrence was conducted taking into account mortality as a competing risk event, with the Fine–Gray[18)] competing risk survival regression model, and presenting the results as sub-hazard ratio (subHR) with a 95% CI. Survival analysis was performed using the Kaplan–Meier method. Values of $p < 0.05$ were considered statistically significant. All analyses were conducted using the SPSS program, except for the competing risks model, that used the R Commander program.

Results

Baseline characteristics

During the study inclusion period, 176 patients underwent mitral repair for functional MR at our center. During the follow-up period, 12 patients (6.8%) were lost, as they had been referred from other health districts.

Table 1 shows the baseline characteristics of the patients included in the study. Mean age was 66.5 ± 9.6 years, 63.6% were male, and 24.4% were diabetic. The etiology of MR was ischemic for 98 patients (55.7%). Concerning ischemic patients, 19.4% had a single-vessel coronary artery disease (CAD), 21.4% had two-vessel CAD, and 59.2% had three-vessel CAD. Complete revascularization by coronary artery bypass grafting was performed in 58.2% of ischemic patients. Concerning nonischemic patients, concomitant of mitral valve repair we performed aortic valve replacement (33.3%), Yacoub aortic valve repair (15.4%), and tricuspid annuloplasty (30.8%). MR grade was II (10.2%), III (43.2%), or IV (46.6%). Baseline LVEF was preserved (>55%) in 40.1% of patients, mildly depressed (45%–55%) in 25.6%, moderately depressed (30%–45%) in 28.5%, and severely depressed (<30%) in 5.8%.

Table 1 Baseline characteristics

n	Total (N = 176)
Age (years)[a]	66.5 ± 9.6
Gender	
Male	112 (63.6%)
Diabetes	40 (24.4%)
Hypertension	92 (52.3%)
Dyslipidemia	83 (53.2%)
Smoking	66 (44.9%)
Renal failure	47 (26.7%)
COPD	28 (19%)
Myocardial infarction	66 (41.5%)
Stroke	12 (7.7%)
Peripheral arterial disease	11 (7.1%)
Atrial fibrillation	77 (48.7%)
Previous cardiac surgery	11 (7.1%)
Euroscore I	9.01 ± 6.85
NYHA class	
I	1 (0.6%)
II	34 (19.5%)
III	104 (59.8%)
IV	35 (20.1%)
MR etiology	
Ischemic	98 (55.7%)
Nonischemic	78 (44.3%)
Coronary artery disease	
Single-vessel	19 (19.4%)
Two-vessel	21 (21.4%)
Three-vessel	58 (59.2%)
Complete coronary artery revascularization	57 (58.2%)
MR grade[b]	
II	18 (10.2%)
III	76 (43.2%)
IV	82 (46.6%)
LVEF	
>55%	69 (40.1%)
45%–55%	44 (25.6%)
30%–45%	49 (28.5%)
<30%	10 (5.8%)

[a]Mean ± standard deviation with 95% CI.
[b]MR grade: II (moderate), III (moderate to severe), and IV (severe).
COPD: chronic obstructive pulmonary disease; NYHA: New York Heart Association; MR: mitral regurgitation; LVEF: left ventricular ejection fraction; CI: confidence interval

Surgical outcomes

Mean cardiopulmonary bypass time was 139.2 ± 45.6 minutes. The median ring size in mitral valve repair was 28 mm (interquartile range 26–30 mm). Perioperative mortality among our sample was 17% (30 patients), and the mean hospital stay was 12.9 ± 9.8 days. We evaluated echocardiographic data (MR grade and left ventricle systolic function) before hospital discharge among patients who survived the perioperative period; it was possible to obtain this data for 97.9% of perioperative period survivors. Residual MR on hospital discharge was grade 0 or 1 for 92.3% of the sample. On hospital discharge, LVEF remained preserved in 47.6% of patients, mildly reduced (LVEF 45%–55%) in 32.2%, moderately reduced (LVEF 30%–45%) in 16.8%, and severely reduced (LVEF <30%) in 3.5%.

Outcomes after follow-up

We conducted a long-term clinical follow-up of a mean 42.2 months (interquartile range 13.4–82.3) and an echocardiographic follow-up of a mean 41.8 months (interquartile range 10.6–79.7). **Table 2** summarizes the

Table 2 Echocardiographic and clinical follow-up

	Total (N = 146)
MR grade[a]	
0	26 (18.4%)
I	63 (44.7%)
II	45 (31.9%)
III	6 (4.3%)
IV	1 (0.7%)
LVEF	
>55%	77 (54.6%)
45%–55%	30 (21.3%)
30%–45%	26 (18.4%)
<30%	8 (5.7%)
NYHA class	
I	43 (30.7%)
II	71 (50.7%)
III	20 (14.3%)
IV	6 (4.3%)
All-cause mortality rate	50 (35%)

[a]MR grade: 0 (absent), I (mild), II (moderate), III (moderate to severe), and IV (severe).
NYHA: New York Heart Association; MR: mitral regurgitation; LVEF: left ventricular ejection fraction

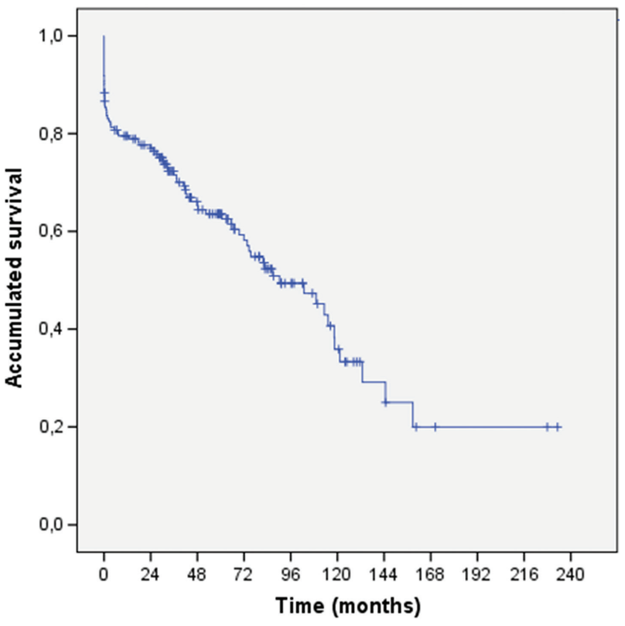

Fig. 1 Cumulative survival after mitral valve repair.

clinical and echocardiographic data at the end of follow-up taking the 146 patients who survived the perioperative period as reference. We observed MR of at least grade II in 52 patients (36.9%), 45 (31.9%) cases with grade II, 6 cases (4.3%) with grade III, and 1 case (0.7%) with grade IV. LVEF remained conserved in 54.6% of patients, and 43 (30.7%) patients were FC I, whereas 71 (50.7%) patients were FC II. **Figure 1** shows the mean survival curve of mortality, with survival at 1, 3, and 5 years of 78.8%, 66.7%, and 52.3%, respectively.

Table 3 shows the univariate analysis for global mortality (perioperative and during follow-up after hospital discharge). The only variables that showed a statistically significant association with mortality were age and LVEF before surgery (dysfunction that was a minimum of mild). Both variables were included in the multivariate analysis, which showed the predictors of mortality as age (HR = 1.038, 95% CI = 1.009–1.067, p = 0.01) and depressed preoperative LVEF (HR = 1.63, 95% CI = 1.018–2.607, p = 0.042).

We performed a competing risk analysis of MR recurrence as an event competing with mortality, as **Table 4** shows, and found age to be the only predictive factor for recurrence of MR in our series (subHR = 1.03, 95% CI = 1.01–1.06, p = 0.02).

Table 3 All-cause mortality univariable analysis

	HR (95% CI)	p
Age	1.038 (1.009–1.067)	0.010
Gender (male)	0.869 (0.554–1.364)	0.542
Diabetes mellitus	0.79 (0.461–1.354)	0.391
Hypertension	1.005 (0.641–1.574)	0.984
Ischemic etiology	0.919 (0.589–1.435)	0.711
Preoperative MR grade IV	1.114 (0.716–1.733)	0.631
Preoperative LVEF <55%	1.667 (1.04–2.671)	0.034
Preoperative NYHA class III–IV	1.336 (0.703–2.539)	0.377
Complete coronary artery revascularization	0.592 (0.326–1.074)	0.085

HR: hazard ratio; CI: confidence interval; MR: mitral regurgitation; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association

Discussion

In our cohort of patients with surgically repaired functional MR (of both ischemic and nonischemic etiology), we observed a recurrence of significant MR (at least grade II) in 36.9% of discharged patients after a mean follow-up of 41.8 months, data that are comparable with those of previous studies such as the 20.3% reported by Petrus et al.[7] or the 32% at 3 years in ischemic MR reported by Dufendach et al.[11] In recent years, the restrictive mechanism surgical technique employed for

Table 4 Predictors of recurrent MR by competing risk analysis

	subHR (95% CI)	p
Age	1.03 (1.01–1.06)	0.02
Gender (male)	1.24 (0.81–1.91)	0.33
Diabetes mellitus	0.69 (0.41–1.13)	0.13
Dyslipidemia	1.01 (0.62–1.63)	0.98
Renal failure	1.03 (0.65–1.63)	0.89
Smoking	0.64 (0.38–1.06)	0.08
COPD	1.28 (0.73–2.23)	0.39
Hypertension	0.66 (0.42–1.02)	0.06
Atrial fibrillation	1.15 (0.72–1.83)	0.56
Stroke	0.66 (0.23–1.86)	0.43
Peripheral arterial disease	1.12 (0.52–2.43)	0.78
Previous cardiac surgery	0.47 (0.14–1.53)	0.21
Ischemic etiology	0.81 (0.53–1.25)	0.35
Preoperative MR grade IV	1.18 (0.77–1.81)	0.46
Preoperative LVEF <55%	1.42 (0.91–2.23)	0.12
Preoperative NYHA class III–IV	1.45 (0.77–2.72)	0.25
Complete coronary artery revascularization	0.57 (0.31–1.06)	0.08

MR: mitral regurgitation; subHR: sub-hazard ratio; CI: confidence interval; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association

mitral repair among patients with functional MR has remained constant: restrictive annuloplasty. Studies such as that of Timek et al.[19] report very low recurrence rates for repaired ischemic MR of around 6% at 5 years. Conversely, other reviews[8–20] calculate more variable rates of significant MR recurrence up to 55%–70% in all likelihood attributable to differences in the baseline characteristics of patients undergoing interventions and to the heterogeneity of surgical techniques employed, which makes it difficult to reach a consensus about a single strategy for the treatment of functional MR.

Recurrence of MR after repair has a significant impact on mortality, as other studies prior to ours have shown (HR = 3.28, 95% CI = 1.87–5.75, p <0.001).[7] In our series, we observed that after a mean follow-up of 42.2 months, survival at 1, 3, and 5 years was 78.8%, 66.7%, and 52.3% respectively. These outcomes contrast with those observed in recent studies of repaired ischemic-etiology MR such as that of Timek et al.[19] or Pang et al.[21] who respectively report around 77% and 69%–71% survival at 5 years. Perioperative mortality among our sample was 17%. Other similar studies calculate variable rates of perioperative mortality such as the 8% of Pang et al.[21] cohort, 6%–13% reported by the meta-analysis of Mihos et al.,[22] or the 8% of mitral valve repair patients until 13% of mitral valve replacement patients reported by Dufendach et al.[11] These data may be related to baseline characteristics of the patients included in our cohort who are older (66.5 ± 9.6 years versus 61.9 ± 9.2 years of Pang et al. cohort)[21] and have frequent comorbidities Euroscore I 9.01 ± 6.85.

In our cohort, the multivariate analysis shows age (HR = 1.038, 95% CI = 1.009–1.069, p = 0.01) and depressed preoperative LVEF (HR = 1.63, 95% CI = 1.018–2.607, p = 0.042) as predictors of mortality. Left ventricle dysfunction bears a close relationship to functional MR, and previous research has shown the association with outcomes of interventions on this valve.[23] In our series, it was related with global mortality, but not with the development of grade II or higher MR in the follow-up.

After performing a competing risk analysis of MR recurrence as a competing event with mortality, the only predictive factor found for the recurrence of significant MR in our series was age (subHR = 1.03, 95% CI = 1.01–1.06, p = 0.016). The analysis of mortality as a competing risk for MR recurrence is not a common feature of recent studies of functional MR,[11] which contributes a clear bias to the predictors of MR recurrence proposed in previous studies. The few previous studies that have evaluated predictors of MR recurrence and taken into account the competing risks model have contributed discrepant results. Some authors have focused on studying the predictors of MR recurrence in echocardiographic parameters of ventricular remodeling such as ventricular diameter,[24] anterior leaflet angle,[25] or the presence of prior myocardial infarction and coaptation distance.[26] Other works, such as that of Kron et al.[27] evaluated MR recurrence prediction models based on clinical and echocardiographic data, including age, sex, EROA, NYHA functional classification, or the presence of CAD. Only the Petrus et al. group[7] performed an analysis of ischemic-etiology MR with heart revascularization surgery, although the results for the predictors of MR recurrence and of mortality were discordant. However, this type of analysis is more frequently employed among degenerative MR series.[28,29]

Nevertheless, our work does have the following limitations. First, it is a single-center, retrospective study (with a small cohort of 176 patients) using data compiled from medical records and limiting the inclusion of patients from other centers and/or those lost to follow-up. On the other hand, we have not conducted a comparison with control group of subjects with dilated cardiomyopathy and functional MR who did not finally undergo intervention. This is partly due to the likely difference in the baseline characteristics and comorbidities of the patients who the Heart Team decided not to operate on, with the consequent bias. Since information was extracted retrospectively from echocardiographic data, only analytical information pertaining to the quantification of MR and LVEF was taken into account, because it was available for all patients. Other echocardiographic parameters related to ventricular morphology (ventricular diameters or volumes[23]) to systolic and diastolic function (tissue Doppler and longitudinal stain rate) and morphological data of mitral valve (such as tenting height[24]) would have been extremely useful to support our conclusions. Finally, we evaluated subjective echocardiographic (recurrence of MR and LVEF) and clinical aspects (functional class), while the assessment of objective prognostic variables (admission for heart failure and cardiovascular mortality) remains pending for future studies.

Conclusion

Mitral repair surgery for functional MR shows heterogeneous outcomes, with age as the only independent predictor of MR recurrence in our series, and age and left ventricle dysfunction the only independent predictors of mortality. These data, in conjunction with better pharmacologic treatment and new transcatheter mitral valve repair methods, could be key in the decision of whether to proceed with surgical intervention in this pathology, optimizing the management of functional MR patients by the Heart Team.

Disclosure Statement

The authors declare no conflicts of interest.

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