Original Article

Recurrent mitral regurgitation after repair of Barlow's disease in a single-center retrospective cohort study

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Background: Barlow's disease (BD) is a common etiology of degenerative mitral valve (MV) disease, often causing significant mitral regurgitation (MR). The pathology of BD is challenging for surgeons performing MV repair (MVR). However, most MVR effectiveness studies have been based on survival and risk of reoperation. The aim of this study was to analyze the safety, efficacy, and durability of MVR in patients with BD and to identify factors that influence recurrent MR.

Methods: We retrospectively analyzed the clinical outcomes of 274 patients undergoing MVR for BD at a tertiary hospital (Guangdong People's Hospital, Guangzhou, China) between January 2010 and June 2022. To analyze the results of MVR and identify the risk factors for MR recurrence, we defined two groups: a total of 240 patients with MR grade <2+ (group A) and a total of 34 patients who had recurrent MR after MVR (group B; the patients with MR ≥2+). All patients were operated on using standard repair techniques. Recurrent MR was the primary outcome. Secondary outcomes were death and reoperation after MVR. Patients were followed up until March 2023. Patients were followed up by clinic visits, telephone calls, and postal or electronic questionnaires.

Results: The median [range] patient age was 46.00 [16–75] years and 186 (67.9%) patients were male. Concomitant procedures were performed in 123 patients: tricuspid valve repair 71 (25.9%), maze or pulmonary vein isolation (PVI) 12 (4.4%), atrial septal defect (ASD) repair 3 (1.1%), and left atrial appendage (LAA) closure 28 (10.2%). Hospital mortality was 0.4%. Long-term complications included radiofrequency ablation in 7 patients (2.6%), pacemaker implantation in 1 patient (0.4%), and stroke in 3 patients (1.1%). The median follow-up was 3.28 (range, 0–12.39) years. Considering the competing risk of mortality, the cumulative incidence of MR progression 2+ or more grades was 2.6%, 5.9%, 14.5%, and 27.7% at 1 month, 1, 5, and 10 years, respectively. Overall survival at 1, 5, and 10 years was 99.3%, 98.6%, and 98.6%, respectively. The immediate postoperative MR area [hazard ratio (HR) =1.723; 95% confidence interval (CI):

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1.051–2.824; P=0.031], postoperative left ventricular end-diastolic dimension (LVEDD) (HR =1.149; 95% CI: 1.016–1.300; P=0.027), and postoperative MR grade {HR = Exp[4.500 – 0.544 × ln(t + 20)]; P=0.008} were associated with an increased risk of MR recurrence, whereas a higher left ventricular ejection fraction (LVEF) (HR =0.931; 95% CI: 0.868–0.999; P=0.049) was associated with a decreased risk.

Conclusions: MVR in patients with BD can be performed with low mortality and complications and is associated with superior long-term outcomes. However, MVR was associated with a certain risk of MR recurrence, especially in those with high postoperative LVEDD, residual MR >1+, and decreased postoperative LVEF. We recommend MVR for patients with BD, especially for those with early-stage disease. However, future randomized controlled trials are needed to confirm this.

Keywords: Barlow's disease (BD); mitral regurgitation (MR); mitral valve repair (MVR); risk of recurrence

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Introduction

Barlow's disease (BD) is one of the more frequent etiologies of degenerative mitral valve (MV) disease, which frequently results in substantial mitral regurgitation (MR) (1). BD caused by excessive myxomatous tissue development with or without calcification is characterized by severe annular dilatation, bileaflet prolapse, and the presence of thick, spongy leaflets (2). The pathology of BD is a challenge for surgeons performing MV repair (MVR), as is the achievement of a durable surgical result in this cohort of patients.

A previous study reported that the linearized recurrence rate of greater than 2+ after surgical repair in patients with degenerative valve disease was 3.7% per year (3). Additionally, the recurrence rate was higher in patients with BD, which was 6.0% per year (4). Similar conclusions have been reached by other authors (5). However, the risk of recurrent MR has not been widely reported because most studies have focused on survival and the risk of reoperation. Of note, the recurrence of regurgitation could only be partially explained by inadequate surgical techniques. Therefore, the aim of this study was to evaluate the outcome, persistence, and survival of MVR in BD and to identify factors influencing recurrent regurgitation. We present this article in accordance with the STROCSS reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1768/rc).

Methods

Study design

Consecutive patients who underwent MVR at a tertiary hospital (Guangdong Provincial People's Hospital, Guangzhou, China) between 1 January 2010 and 1 June 2022 were retrospectively studied. The study was approved by the Institutional Review Board at Guangdong Provincial People's Hospital (No. KY-Q-2021-271-02; 2022.1.29 approval) and conformed to the Declaration of Helsinki (as revised in 2013). The requirement for obtaining informed consent was exempted due to the retrospective nature of the study with minimal risk. The research was retrospectively registered.

Patient population

Between 1 January 2010 1 and June 2022, a total of 282 consecutive patients with BD underwent MVR at our clinic. However, eight patients with unsuccessful MVR procedures were excluded [one patient was found to have MR >2+ on saline testing and seven patients were found to have MR >2+ on transesophageal echocardiography (TEE), one of whom had systolic anterior motion (SAM); all the eight patients were referred for MV replacement surgery] (*Figure 1*), and 274 patients were studied. To analyze the results of MVR and to identify the risk factors affecting MR

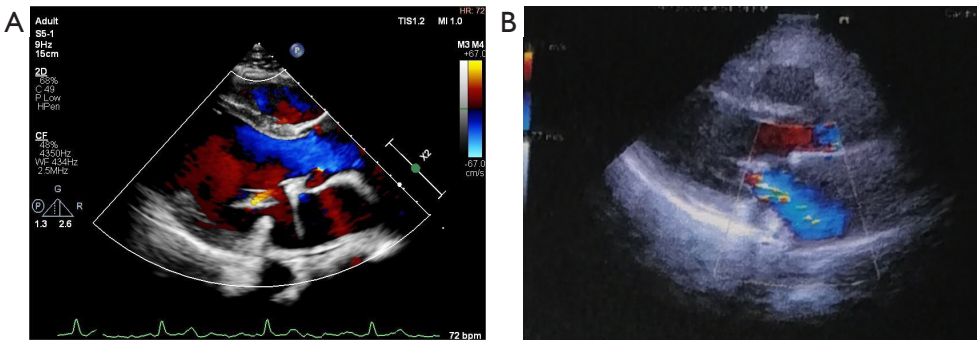


Figure 1 Echocardiographic images of successful and unsuccessful procedures. (A) Successful MVR procedure; (B) unsuccessful MVR procedure. 2D, two-dimensional; CF, color flow; WF, wall filter; TIS, thermal index of soft tissue; MI, mitral insufficiency; MVR, mitral valve repair.

recurrence, we defined two groups: a total of 240 patients had MR grade <2+ (group A), whereas 34 patients experienced recurrent MR after MVR (group B; the patients who had MR ≥2+). Baseline clinical and echocardiographic characteristics (at the time of preoperative evaluation) of these patients were compared between the two groups (*Table 1*).

MVR patients who underwent concomitant tricuspid valve repair (TVR), maze/pulmonary vein isolation (PVI), left atrial appendage (LAA) closure, or atrial septal defect (ASD) repair were also included in this study. Patients ≤14 years of age, those with cardiomyopathy, cardiac tumors, previous cardiac surgery, concomitant aortic surgery, concomitant coronary artery bypass grafting (CABG), and redo surgery for a failed MVR were excluded (*Figure 2*).

Smokers were required to quit smoking for 1 month before surgery, diabetics were required to control their blood sugar, and all patients underwent coronary computed tomography (CT) or coronary angiography and fecal occult blood testing to reduce the risk of surgery.

MV characteristics

The degenerative MV was classified as BD based on echocardiographic and intraoperative visual findings (6).

Surgical techniques

All patients underwent intraoperative echocardiography before and after repair. Standard cannulation techniques using central or peripheral cannulation (depending on the surgical approach used) and intermittent cold blood cardioplegia to protect the heart were used in all cases. MVR was performed via a median sternotomy (MS) in 55.1% of patients and via a totally endoscopic minimally invasive (TEMI) approach in 44.9% of patients. Surgery performed by different surgeons in the same center; each cardiac surgeon had >15 years of experience and conducted >50 MVR procedures per year.

All of the patients were operated on using standard repair techniques. Due to the extensive mitral lesions in patients with BD, a combination of repair techniques is often required. Due to their complex pathology, these valves are technically more challenging. The aims of reconstructive surgery are to preserve or restore normal leaflet motion, create a large coaptation surface, and stabilize the entire annulus with a remodeling annuloplasty (7). It is well known that reconstruction can be achieved by resection of the prolapsing segments, commissuroplasty, implantation of neochordae, or annuloplasty. In this study, posterior leaflet (PL) prolapse was preferably corrected by resection if the prolapsing segment had extensive overgrowth. The prolapse of the anterior leaflet (AL) was corrected by transfer of the chordae or implantation of an artificial chordae. If there was no dilatation or only a slight dilatation of the annulus, the prolapse was preferably corrected by artificial chordae. In the majority of instances, mitral ring annuloplasty was performed to complete the repair, with the exception of extreme circumstances, such as where the AL was too large and SAM may be anticipated following ring annuloplasty, or when the annulus was not or just slightly dilated. For the selection of the ring size, the intertrigonal distance and the AL height were measured. The ring was chosen according to the surgeon's discretion. The competence of the valve after the repair was assessed by the saline test and then by TEE after the atrium had been closed. If the residual MR was more

Table 1 Clinical and echocardiographic characteristics (at the preoperative echocardiographic assessment) of the two repair groups

Variables	Total cohort (n=274)	Group A (n=240)	Group B (n=34)	P value
Age (years)	46.00 [16–75]	43.00 [16–75]	51.50 [18–71]	0.180
Male	186 (67.9)	159 (66.3)	27 (79.4)	0.124
BMI (kg/m^2)	22.13±3.54	22.07±3.46	22.53±4.15	0.475
NYHA class (III/IV)	58 (21.2)	51 (21.3)	7 (20.6)	0.443
Comorbid disease				
Hypertension	47 (17.2)	42 (17.5)	5 (14.7)	0.686
Diabetes	9 (3.3)	8 (3.3)	1 (2.9)	>0.999
Coronary artery disease	9 (3.3)	7 (2.9)	2 (5.9)	0.364
AF	45 (16.4)	37 (15.4)	8 (23.5)	0.232
Stroke	6 (2.2)	5 (2.1)	1 (2.9)	0.552
Chronic kidney disease	0 (0.0)	0 (0.0)	0 (0.0)	–
Endocarditis	13 (4.7)	9 (3.8)	4 (11.8)	0.063
Preoperative MV assessment (echocardiogram)				
Preoperative MR grade (3+/4+)	269 (98.2)	237 (98.8)	32 (94.1)	0.817
Preoperative TR grade (3+/4+)	31 (11.3)	28 (11.7)	3 (8.8)	0.654
LAD (mm)	45.01±9.08	44.08±8.48	51.62±10.49	<0.001
LVEDD (mm)	57.06±7.13	56.56±6.46	60.59±10.19	0.031
LVESD (mm)	34.18±5.88	33.65±5.42	37.91±7.56	0.003
LVESD ≥40 mm	35±12.8	26±10.8	9±26.5	0.023
RAD (mm)	48.36±8.61	48.43±8.68	47.85±8.17	0.714
RVD (mm)	53.57±6.42	53.55±6.54	53.74±5.58	0.873
LVEF (%)	66.72±6.02	66.90±6.00	65.44±6.40	0.188
Intraoperative MV assessment (surgery view)				
Prolapsing segments	3.00 [0–8]	3.00 [0–8]	3.00 [1–8]	0.862
Anterior	57 (20.8)	47 (19.6)	10 (29.4)	0.186
Posterior	99 (36.1)	87 (36.3)	12 (35.3)	0.914
Anterior and posterior	122 (44.5)	109 (45.4)	13 (38.2)	0.430
Perforation or fissure	21 (7.7)	17 (7.1)	4 (11.8)	0.309
Rupture of the chordal	125 (45.6)	109 (45.4)	16 (47.1)	0.857

Data are presented as the median [range], mean ± SD, or n (%). Group A: defined as patients who had MR grade <2+; group B: defined as patients who had recurrent MR after MVR, that is, patients with MR grade ≥2+. BMI, body mass index; NYHA, New York Heart Association; AF, atrial fibrillation; MV, mitral valve; MR, mitral regurgitation; MVR, mitral valve repair; TR, tricuspid regurgitation; LAD, left atrium dimension; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; RAD, right atrium dimension; RVD, right ventricular dimension; LVEF, left ventricular ejection fraction; SD, standard deviation.

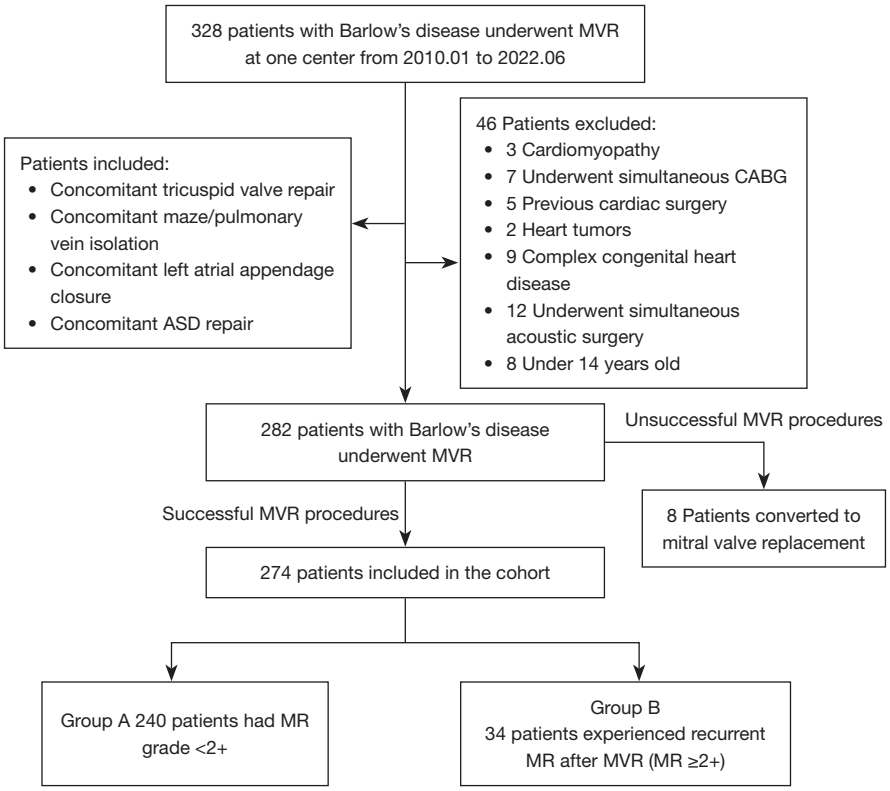


Figure 2 Flow chart of the inclusion and exclusion criteria for all cohorts. Group A: defined as patients who had MR grade <2+; group B: defined as patients who had recurrent MR after MVR, that is, patients with MR grade ≥2+. MVR, mitral valve repair; ASD, atrial septal defect; CABG, coronary artery bypass grafting; MR, mitral regurgitation.

than mild, a second pump run was performed for repair.

For each patient, the specific surgical repair techniques used at the end of surgery were identified and coded: leaflet intervention (none, resection, cleft closure), annulus intervention (none, sliding repair), neochordae implantation (yes or no), and annuloplasty ring placement (yes or no).

Table 2 shows the operative details. The most common repair techniques were artificial chordae implantation and mitral annuloplasty. Edge-to-edge repair was performed as the primary repair strategy in 3.3% of patients. Cleft closure/plication (17.9%) and resection (15.7%) were rarely used. The AL procedure was performed in 20.8%, the PL procedure in 36.1%, and the bileaflet procedure in 44.5%.

Nearly all of the patients (99.3%) received annuloplasties. The Carpentier-Edwards (CE) Physio ring (Physio) (Edwards Lifesciences Corp., Irvine, CA, USA) was used in 246 (89.8%) patients, whereas 13 (4.7%) patients received the CE Physio II ring.

Concomitant tricuspid surgery was performed in 71 patients (25.9%), LAA closure was performed in 28 patients (10.2%), and the A maze procedure or PVI was performed in 12 patients (4.4%). The mean time for cardiopulmonary bypass (CPB) was 147.43 minutes, and the mean time for aortic cross-clamp (ACC) was 98.24 minutes.

Follow-up

The follow-up was performed until March 2023. During a median follow-up time of 3.28 years, patients were followed up by means of clinic visits, phone calls, mailed or electronic questionnaires. Clinical and echocardiographic follow-up were performed by the referring cardiologist. Survival, reoperation, cerebrovascular events, bleeding complications, anticoagulation therapy, New York Heart Association (NYHA) functional class, and heart rhythm were recorded.

End points and echocardiographic measures

The primary outcome was recurrent MR which was determined on postoperative transthoracic echocardiography

Table 2 Operative outcomes of the total cohort and the two groups

Variables	Total cohort (n=274)	Group A (n=240)	Group B (n=34)	P value
Approach				0.116
MS	151 (55.1)	128 (53.3)	23 (67.6)	
TEMI	123 (44.9)	112 (46.7)	11 (32.4)	
Concurrent procedure				
TVR	71 (25.9)	59 (24.6)	12 (35.3)	0.182
Maze/PVI	12 (4.4)	11 (4.6)	1 (2.9)	>0.999
ASD repair	3 (1.1)	1 (0.4)	1 (2.9)	0.233
LAA closure	28 (10.2)	24 (10.0)	4 (11.8)	0.762
Repair techniques				
Resection and suture	43 (15.7)	36 (15.0)	7 (20.6)	0.402
Sliding	3 (1.1)	2 (0.8)	1 (2.9)	0.329
Neochordal replacement	231 (84.3)	202 (84.2)	29 (85.3)	0.866
Number of cord tendons implanted	3.16±2.79	3.31±2.37	3.53±2.48	0.613
Mitral annuloplasty ring	272 (99.3)	238 (99.2)	34 (100.0)	>0.999
Mitral annuloplasty ring type				0.748
Physio	246 (89.8)	215 (89.6)	31 (91.2)	
Physio II	13 (4.7)	12 (5.0)	1 (2.9)	
Medtronic	3 (1.1)	3 (1.3)	0 (0.0)	
Balance medical	10 (3.6)	8 (3.3)	2 (5.9)	
Size of mitral annuloplasty (mm)	32.41±4.64	32.41±4.80	32.48±3.27	0.976
Big size of mitral annuloplasty	n=272	n=239	n=33	0.039
Big size ≥34	111 (40.8)	103 (43.1)	8 (24.2)	
Small size <34	161 (59.2)	136 (56.9)	25 (73.5)	
Commissuroplasty	49 (17.9)	44 (18.3)	5 (14.7)	0.605
Edge-to-edge	9 (3.3)	8 (3.3)	1 (2.9)	>0.999
Intraoperative MR area (cm^2)	0.37±0.59	0.34±0.59	0.56±0.58	0.045
CPB time (min)	147.43±40.20	148.92±41.22	136.26±30.25	0.035
ACC time (min)	98.24±32.68	99.48±33.40	89.50±25.81	0.048
Total operation time (min)	240.47±57.61	240.75±59.22	238.50±45.28	0.832
ICU time (hours)	49.26±78.26	48.97±80.94	51.29±56.71	0.871
MVT (hours)	18.15±40.07	17.27±37.54	24.35±55.03	0.335
LOS (days)	9.10±7.52	8.95±7.42	10.15±8.25	0.386

Table 2 *(continued)*

Table 2 *(continued)*

Variables	Total cohort (n=274)	Group A (n=240)	Group B (n=34)	P value
Postoperative MV assessment (echocardiogram 1 week after surgery)				
MR grade (3+/4+)	9 (3.3)	2 (0.8)	7 (20.6)	<0.001
LAD (mm)	36.02±7.04	35.56±6.85	39.21±7.60	0.005
LVEDD (mm)	47.43±7.08	46.79±6.43	52.65±9.77	<0.001
LVESD (mm)	31.77±6.81	31.11±6.20	36.38±8.94	<0.001
LVEF (%)	59.40±7.66	59.79±7.79	55.71±9.23	0.006

Data are presented as the mean ± SD or n (%). Group A: defined as patients who had MR grade <2+; group B: defined as patients who had recurrent MR after MVR, that is, patients with MR grade ≥2+. MS, median sternotomy; TEMI, total endoscopic minimally invasive; TVR, tricuspid valve repair; PVI, pulmonary vein isolation; ASD, atrial septal defect; LAA, left atrial appendage; MR, mitral regurgitation; MVR, mitral valve repair; CPB, cardiopulmonary bypass; ACC, aortic cross-clamp; ICU, intensive care unit; MVT, mechanical ventilation time; LOS, length of hospital stay; MV, mitral valve; LAD, left atrium dimension; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; SD, standard deviation.

(TTE). The secondary outcomes were death and MV reoperation after surgery. Recurrence was measured by TTE and verified by the Echo Core laboratory. Recurrent MR was defined as MR grade ≥2+. The severity of MR was classified using Grades (grade 0, 1+, 2+, 3+, 4+) (8). To be classified as having no recurrent MR, patients with some missing echocardiographic data had to have MR <2+ on at least two recent echocardiograms. If the patient had recurrent MR, the TTE result was based on the information from the time that the MR ≥2+ first occurred; the recurrence time was the date that the MR ≥2+ was first identified, and the reoperation time was the date that the reoperation was performed. In addition, factors affecting MR recurrence were analyzed by dividing patients into a group undergoing MVR via MS and MVR via TEMI. Pre, intra, and postoperative echocardiographic data were collected.

Statistical analysis

Categorical variables are presented as frequencies with percentages and were compared between groups using Fisher's exact test. Continuous variables are presented as the means with standard deviation (SD) and were compared between groups using analysis of variance. The Shapiro-Wilk test was utilized for the normality test. Cox proportional hazards methods were used to analyze the data on the recurrence of MR over time. The Kaplan-Meier method was used to analyze time-to-event data on survival, recurrent MR, and MV reoperation, and the log-rank and Wilcoxon test were used for group comparisons. Estimates are presented with 95% confidence intervals (CIs). Statistical significance was indicated by two-sided P values <0.05. Missing data were filled in using the mean value. As the rate of loss to follow-up in this study was less than 5%, data for loss to follow-up were corrected by processing using the last observation carried forward (LOCF) method. All statistical analyses were performed using R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 23.0 (IBM Corp., Armonk, NY, USA).

Results

Immediate surgical result of MVR

The most common preoperative comorbidities were hypertension (17.2%) and atrial fibrillation (AF) (16.4%), and 21.2% were in advanced NYHA functional class (III or IV). The immediate postoperative echocardiographic results were excellent: 270 patients (98.5%) had no or MR =1+. The in-hospital mortality rate was 0.4%, which was due to death from sepsis with multiple organ failure. The success of the operation was assessed by an echocardiographic examination of the function of the MV within the first postoperative week. MR was absent or trivial in 95.4% of all patients at 1 week postoperatively. No cases of endocarditis were documented.

The most common postoperative complications were lung infection in 18 (6.6%), reoperation for bleeding in 11 (4.0%), arrhythmia in 4 (1.5%), gastrointestinal bleeding in 3 (1.1%), renal dysfunction in 3 (1.1%), and stroke in 3 (1.1%) patients (*Table 3*). The mean intensive care unit

Table 3 Operative complications of the total cohort and the two groups

Variables	Total cohort (n=274)	Group A (n=240)	Group B (n=34)	P value
Perioperative complications, n (%)				
Death	1 (0.4)	1 (0.4)	0 (0.0)	>0.999
Reoperation for bleeding	11 (4.0)	10 (4.2)	1 (2.9)	>0.999
Arrhythmia	4 (1.5)	4 (1.7)	0 (0.0)	>0.999
Gastrointestinal bleeding	3 (1.1)	2 (0.8)	1 (2.9)	0.329
Renal dysfunction	3 (1.1)	3 (1.3)	0 (0.0)	0.182
Stroke	3 (1.1)	2 (0.8)	1 (2.9)	0.329
Lung infection	18 (6.6)	17 (7.1)	1 (2.9)	0.709
Low cardiac output	7 (2.6)	6 (2.5)	1 (2.9)	>0.999
Long-term complications, n (%)				
Radiofrequency ablation	7 (2.6)	6 (2.5)	1 (2.9)	>0.999
Pacemaker implantation	1 (0.4)	1 (0.4)	0 (0.0)	>0.999
Stroke	3 (1.1)	1 (0.4)	2 (5.9)	0.041
Recurrent MR	34 (12.4)			
MV reoperation	4 (1.5)			
Death	3 (1.1)			

Group A: defined as patients who had MR grade <2+; group B: defined as patients who had recurrent MR after MVR, that is, patients with MR grade ≥2+. MR, mitral regurgitation; MVR, mitral valve repair; MV, mitral valve.

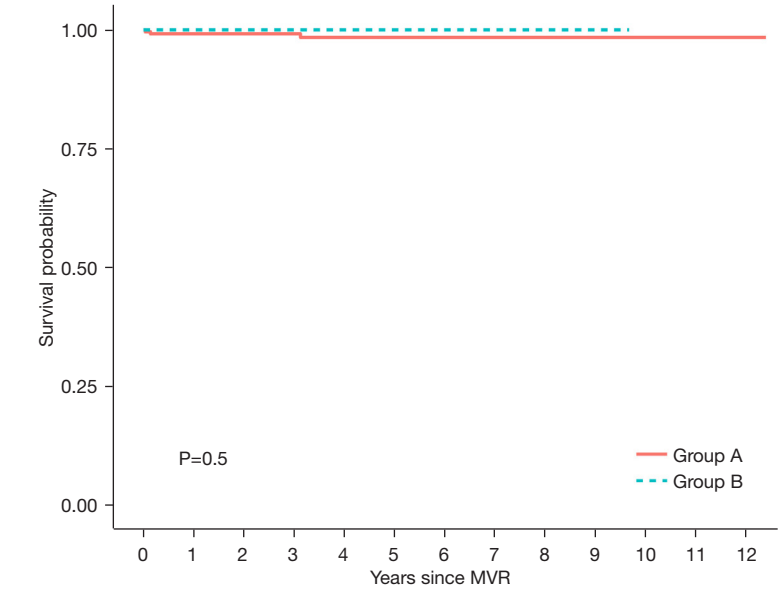
(ICU) stay was 49.26 hours. The mean length of hospital stay (LOS) was 9.10 days (*Table 2*).

Survival and recurrent rate

During a median follow-up time of 3.28 years (range, 0–12.39 years). A total of eight patients were lost to clinical follow-up, mainly due to the fact that these eight patients did not return to our center after surgery and neither the patients nor their families could be contacted through contact telephone numbers and addresses. Over time, a total of three patients died, all of whom were in the A group. There was one case of death due to cardiogenic causes. There was no difference in survival between patients without MR recurrence and those who had MR recurrence (P=0.5) (*Figure 3*). Overall survival rates were 99.3%±0.5% at 1 year, 98.6%±0.8% at 5 years, and 98.6%±0.8% at 12 years. During the follow-up period, 34 patients had moderate or higher MR. Some 87.6% of valves were functional (MR <2+) at the end of follow-up on 1 March 2023 (up to 12 years). The cumulative incidence rate of MR ≥2+ at 12 years was 12.4%. According to the classical Kaplan-Meier approach, freedom from recurrent MR (regurgitation <2+) was 97.4%±1.0% at 1 month, 94.1%±1.4% at 1 year, 85.3%±2.6% at 5 years, and 72.0%±8.2% at 10 years (this analysis did not account for death as a competing outcome, death counted as a censor). When we considered competing risks due to mortality, the cumulative incidence of MR progression of 2+ or more grades was 2.6%, 5.9%, 14.5%, and 27.7% at 1 month, 1 year, 5 years, and 10 years, respectively. Of note is the slightly higher rate of recurrent MR after the first 6 months postoperatively, with a cumulative incidence of MR ≥2+ at 6 months of 5.5%. During the follow-up period, 4 patients (1.5%) underwent MV reoperation. The freedom from reoperation was 100% at 1 year, 98.9%±0.8% at 5 years, 89.1%±6.6% at 10 years, and 89.1%±6.6% at 12 years for all patients. *Figure 3* illustrates the main findings of the study.

Clinical outcome and morbidity

A total of seven patients who underwent radiofrequency ablation had a recurrence of AF, and one other received a pacemaker implantation during the follow-up period. There were three cases of stroke (*Table 3*).



Group A													
At risk	240	224	185	140	107	67	28	22	14	9	3	2	1
Censored	0	14	53	98	130	170	209	215	223	228	234	235	236
Events	0	2	2	2	3	3	3	3	3	3	3	3	3
Survival probability	0.992	0.992	0.992	0.985	0.985	0.985	0.985	0.985	0.985	0.985	0.985	0.985	0.985
Group B													
At risk	34	32	31	23	17	14	7	5	3	1	0	0	0
Censored	0	2	3	11	17	20	27	29	31	33	34	34	34
Events	0	0	0	0	0	0	0	0	0	0	0	0	0
Survival probability	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

Figure 3 Cumulative incidence of deaths in the overall cohort of patients with and without recurrent MR. Group A: defined as patients who had MR grade <2+; group B: defined as patients who had recurrent MR after MVR, that is, patients with MR grade ≥2+. MVR, mitral valve repair; MR, mitral regurgitation.

Predictive factors of recurrent MR after MVR

To analyze the results of MVR and to identify the risk factors affecting MR recurrence, we defined two groups: no MR recurrence (group A, n=240) and MR recurrence (group B, n=34). Patients with recurrent MR had a larger left atrium dimension (LAD) (P<0.001) and left ventricular end-diastolic dimension (LVEDD) (P=0.031) on preoperative echocardiography. In addition, a larger left ventricular end-systolic dimension (LVESD) (P=0.003) and a higher proportion of LVESD ≥40 mm (P=0.023) were found in patients with MR recurrence. In patients with MR recurrence, the number of prolapsing MV segments was not significantly higher than that in the group without MR recurrence. Furthermore, the proportions of posterior and anterior MV leaflets were not significantly larger in patients with MR recurrence than in patients without MR recurrence. In addition to these findings, 125 patients (45.6%) had ruptured chordae tendineae, 21 patients (7.7%) had one or more clefts, and 13 patients (4.7%) had endocarditis. There was no significant difference between the two groups (*Table 1*).

Of note, specific surgical repair techniques had no significant predictive value for recurrent regurgitation: the use of sliding annuloplasty (P=0.329), resection (P=0.402), annuloplasty ring (P>0.999), and chordal replacement (P=0.866) were generally not associated with outcome. Almost all patients received an annuloplasty ring (n=272, 99.3%). However, the distribution of annuloplasty ring size and type was not significantly different between the two groups (*Table 2*).

Multivariable time-dependent Cox proportional hazards analysis (*Table 4*) revealed that the subpopulation with regurgitation recurrence was mainly characterized by a

Table 4 Univariate and stepwise multivariate Cox hazard analysis of risk factors for recurrent MR ≥2+

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Preoperative LAD	1.071 (1.041–1.101)	<0.001	–	–
Preoperative LVEDD	1.061 (1.024–1.099)	0.031	–	–
Preoperative LVESD		0.003		
Preoperative LVESD ≥40 mm	2.842 (1.325–6.097)	0.023	–	–
Postoperative LVEF	0.911 (0.831–0.098)	0.046	0.931 (0.868–0.999)	0.049
Postoperative LAD	1.073 (1.028–1.120)	0.001	–	–
Postoperative LVEDD	1.089 (1.053–1.126)	<0.001	1.149 (1.016–1.300)	0.027
Postoperative LVESD	1.093 (1.052–1.135)	<0.001	–	–
Intraoperative MR area	1.383 (0.968–1.976)	0.047	1.723 (1.051–2.824)	0.031
Degree of postoperative MR	4.810 (2.712–8.530)	<0.001	Exp[4.500 – 0.544 × ln(t + 20)]	0.008

MR, mitral regurgitation; HR, hazard ratio; CI, confidence interval; LAD, left atrium dimension; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction.

Table 5 Multivariable analysis for recurrent MR with patients via MS or TEMI

Variables	MS		TEMI	
	HR (95% CI)	P value	HR (95% CI)	P value
Postoperative LVEF	0.911 (0.831–0.999)	0.046	–	–
Degree of postoperative MR	Exp[321.40 – 0.515 × ln(t + 20)]	0.023	–	–
Concurrent ASD repair	–	–	13.780 (1.014–187.336)	0.049

MR, mitral regurgitation; MS, median sternotomy; TEMI, total endoscopic minimally invasive; HR, hazard ratio; CI, confidence interval; LVEF, left ventricular ejection fraction; ASD, atrial septal defect.

higher grade of 1 week postoperative MR {hazard ratio (HR) = Exp[4.500 – 0.544 × ln(t + 20)]; P=0.008}. The intraoperative MR area [HR =1.723; 95% confidence interval (CI): 1.051–2.824; P=0.031] and postoperative LVEDD (HR =1.149; 95% CI: 1.016–1.300; P=0.027) showed a trend towards higher recurrence of regurgitation. Additionally, postoperative left ventricular ejection fraction (LVEF) also predicted regurgitation recurrence, with a protective effect (HR =0.931; 95% CI: 0.868–0.999; P=0.049).

When the patient population was divided into those who underwent MVR via MS and those who underwent MVR via TEMI, the risk factors became more focused (*Table 5*). In the MS approach, the grade of postoperative MR was predictive of the recurrence of regurgitation (P=0.023) as well as the LVEF of the postoperative period (P=0.046). In patients treated via the TEMI approach, the concomitance of ASD repair (P=0.049) was the main predictor of regurgitation.

Discussion

There is still an ongoing debate about the durability of MVR for patients with BD. Valve repair in BD is particularly challenging due to its complex pathology. Multisegmental involvement with excess leaflet tissue results in a lack of a reference point, complicating valve analysis and repair planning. Our study demonstrated that in a single institution, real-world population with BD, a high rate of successful reconstruction with low morbidities and mortalities, excellent long-term survival, and low reoperation rates could be achieved. Our high successful repair rate of 95.7% in a cohort with complex valve pathology compared favorably with other studies that report

repair rates of 90–100% depending on the valve pathology (9-11). Repair rate in prior studies was reported as 99% and 100% by Faerber *et al.* (12) and Tomšic *et al.* (13), respectively. Faerber *et al.* analyzed the post-operative results of symmetrical and asymmetrical lesions according to repair technique in 103 patients with BD (12). In our study, we enrolled all BD patients who underwent MVR, without bias towards the surgical technique to be more in line with clinical reality, and analyzed the associated risk factors affecting postoperative survival, reoperation, and recurrent regurgitation. We found an excellent clinical outcome with a low reoperation rate (89.1% freedom) at 10 years. Nevertheless, the rate of freedom from failed repair (regurgitation <2+) was 72.0% at 10 years. Meanwhile, the present article confirmed previous findings that the recurrence of MR based on echocardiographic studies was more frequent than the reoperation rate indicates. Reoperation rate was therefore shown not to be the best parameter to estimate the efficacy and durability of MVR.

MV pathology

As mentioned earlier, our immediate postoperative echocardiographic results were excellent: 98.5% of the patients had no or MR =1+. However, despite such a highly successful repair, recurrence of MV incompetence still occurred at a constant rate during the following years. The causes of the recurrence of regurgitation after MVR can be classified as either procedure-related or valve-related. There is a reported difference in outcome within the MV patient population, depending on valve pathology: the literature shows excellent long-term outcomes for PL patients and less good outcomes for AL and bileaflet. In a larger study, they showed that patients with an isolated AL prolapse had an increased early risk of reoperation (14). However, in our study, we did not find any differences between the prolapsed segments; therefore, we are convinced that either AL or PL prolapse were not significantly associated with the recurrence of regurgitation, as already shown by Passos *et al.* (15) and De Bonis *et al.* (16).

Surgical repair techniques

A wide variety of surgical repair techniques have been described in the 40 years since MVR for MR was successfully performed (17). Many different MVR techniques were used in the present study. It is known from previous literature that the implantation of artificial chordae (18) and the use of ring annuloplasty (19) reduced the risk of recurrent MR in the late hazard phase. Pfannmueller *et al.* reported more MR at discharge in the resection group than in the chordae group (20). The artificial chordae technique is associated with excellent results and may therefore be more durable (9). Kasegawa *et al.* showed that the number of artificial chordal replacements was associated with a reduced risk of recurrent moderate MR (21). Of note, in the present study, the neochordae group did not have such superior outcomes. There were no significant differences between the resection group and the neochordae group, and the number of chordae implanted was not associated with the reduced recurrence of MR. This study suggests that neochordae and resection techniques are equally safe and effective.

Recently, several groups have reported excellent clinical results with simple ring-only repair in patients with BD (12). Lawrie *et al.* found that leaflet repair was not needed in 17% of patients with BD (22). In previous studies, Hiemstra *et al.* and van Wijngaarden *et al.* reported that annular abnormalities of the MV were already present prior to the development of significant MR (23,24). Ben Zekry *et al.* reported excellent mid-term clinical results of ring-only repair in patients with BD, with no recurrence of MR during a mean follow-up period of 38±36 months (25). In addition, Adams *et al.* mentioned that the use of large annuloplasty rings has recently been advocated with regard to the risk of SAM (26). The present study showed that the size and type of annuloplasty rings had no relevance to the risk of recurrence of regurgitation and did not involve any patients with SAM. Although Physio II is considered an improvement over Physio, it has an improved shape, a double saddle, and a cuff to reduce tension on the sutures. However, better annular dynamics seen in Physio II annuloplasty do not translate into superior freedom from recurrent MR. The type of annuloplasty device does not influence the long-term results that have previously been reported (27,28). Therefore, in terms of procedural or surgical factors, our study found no factors associated with recurrence of MR. Meanwhile, the use of annuloplasty rings (99.3%) and the implantation of artificial chordae (84.3%) in most patients may explain the good clinical outcomes in our results. Our study has shown that the technique of artificial chordae with a ring annuloplasty can give excellent results (29,30).

Despite the fact that patients with BD underwent more complex repairs with significantly longer operative, CPB, and ACC times, this study demonstrated very acceptable 10-year freedom from reoperation (89.1%) and 10-year

survival (98.6%) rates. According to our data, the long-term survival rate of 98.6% is comparable to or better than that of other studies, which ranged from 66% to 85% (14,31). Furthermore, our in-hospital mortality (0.4%), stroke (1.1%), and rethoracotomy (4.0%) rates are low and comparable to other studies (20,32). The mean LOS was 9.10 days, and there were no significant differences between the groups. However, our LOS is shorter than that in other studies (32).

MS versus TEMI

In the present study, the difference in surgical approach was not associated with recurrent MR ≥2+. The TEMI technique can be proposed in cases of complex MV disease. Recent studies have shown that the safety and efficacy outcomes of the TEMI approach are equivalent to those of conventional MS surgery (33). Sakaguchi *et al.* and De Bonis *et al.* demonstrated that MVR in patients with BD also provides excellent results via a minimally invasive approach (34,35). TEMI MV surgery can also provide patients with a cosmetically pleasing incision, faster recovery, and a faster return to normal activities (36). Meanwhile, we found that the grade of postoperative MR and LVEF were predictive of the recurrence of regurgitation in the MS approach. In patients treated via the TEMI approach, the concomitance of ASD repair is the main predictor of regurgitation; however, all (three patients) who underwent TEMI were in group B. Follow-up research is needed to clarify whether it is of real significance.

Recurrence and risk factors

MVR is not indicated in all patients with BD, and performing MVR in unsuitable patients would increase the risk of mortality and postoperative recurrence. Durability is the main concern regarding MVR in patients with BD. Previous studies have shown a higher recurrence rate after MVR (4). In our cohort, 87.6% of valves were functional (MR <2+) at the end of follow-up on 1 March 2023 (up to 12 years). This is similar to or better than in other studies that have reported up to 89% in long-term follow-up (9,14). In the multivariate Cox analysis, our study showed that independent predictors of MR recurrence included immediate postoperative MR area, postoperative LVEF, LVEDD, and postoperative MR grade (all P<0.05), and postoperative LVEF was protective (HR =0.931; 95% CI: 0.868–0.999). The present study found that elevated postoperative LVEDD (HR =1.149; 95% CI: 1.016–1.300) and decreased postoperative LVEF showed a trend towards higher recurrence of regurgitation. Previous studies have noted that left ventricular (LV) systolic dysfunction is the ultimate adverse outcome of chronic MR and is the leading cause of postoperative mortality in MVR (37,38). Nappi *et al.* identified a preoperative LVEDD >62 mm as an independent predictor of poor outcome (39). In addition, LVEF <40% increased the risk of recurrent moderate or severe MR, as shown by David *et al.* (14) This may be because long-term chronic MR leads to irreversible remodeling of the LV and because LV dysfunction may persist into the postoperative period, thus affecting postoperative recovery. Patients with severe MR, even if asymptomatic, should therefore be recommended for surgical repair as soon as possible. Furthermore, Morisaki *et al.* showed that the independent risk factors for moderate to severe recurrent regurgitation in a previous study of 362 patients who underwent successful MVR were residual regurgitation ≥ mild (29). This finding suggests that MVR may be the optimal choice for patients with BD after careful selection, particularly in the early stages of BD with predominant MR. Careful assessment of LV function and residual MR by experienced surgeons may be crucial for durable MVR in patients with BD. However, considering the differences in patient characteristics, this result might be statistically overestimated. Further studies should be performed in the future to investigate these factors.

Study limitations

This study did have some inherent limitations. It was a retrospective observational study, single-center, and uncontrolled, which allows for potential bias. Moreover, for both groups of patients, most of the cases were censored. Such a high level of censored data makes the available results highly biased, which affects the credibility of the results. This is one of the main limitations of the study. Further large randomized controlled trials with long-term follow-up are needed to determine the feasibility of MVR in patients with BD.

Conclusions

According to our study, MVR for patients with BD presented a beneficial survival effect. However, MVR was associated with a certain risk of MR recurrence, especially in those with high postoperative LVEDD, residual MR >1+, and decreased

postoperative LVEF. We recommend MVR for patients with BD, especially for those with early-stage disease.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Institutional Review Board at Guangdong Provincial People's Hospital (No. KY-Q-2021-271-02; 2022.1.29 approval) and conformed to the Declaration of Helsinki (as revised in 2013). The requirement for obtaining informed consent was exempted due to the retrospective nature of the study with minimal risk.

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