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ORIGINAL ARTICLE

Mitral valve repair in infective endocarditis is not inferior to valve replacement: results from a Spanish nationwide prospective registry

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Abstract

Introduction Infective endocarditis (IE) still carries high morbidity and mortality and frequently requires surgery. The benefit of mitral valve repair (MVr) in the setting of IE is yet to be proven. The goal of this study was to assess the results of MVr in patients with IE after a minimum follow-up of 1 year.

Methods This study is based on a Spanish nationwide prospective registry that included patients operated on for native mitral valve IE. The collaborating Institutions pooled their pre-, peri-, and postoperative data into the database of the GAMES group [Grupo de Apoyo al Manejo de la EndocarditiS (Group for support and management of infective endocarditis)].

Results Data from 27 hospitals were recorded and 3524 cases of active IE identified between 2008 and 2016. There were 1513 cases of mitral IE, of which 898 involved native valves. Of these, 437 patients underwent surgical treatment, and 369 completed the 1-year follow-up. The valve was repaired in 68 cases (18.4%). Preoperative groups were comparable (EuroSCORE MVr 7.7 vs MVR 8.0; p = ns). Mortality in the repair group was inferior to that in the replacement group (16.2% vs 27.2%, $p = 0.058$). At 1 year, mortality remained higher in the replacement group: 3.7% vs 2.9%. Relapse of the infection was slightly more frequent in the repair group (7.1% vs 3.7%; p = ns), although this did not lead to higher rates of reintervention (MVr/MVR: 2.9% vs 4.9%).

Conclusion MVr is an attractive option for specific patients with IE and does not seem to negatively impact on relapses.

Keywords Infectious endocarditis · Mitral valve reparation · Mitral valve replacement · Cardiac surgery

Introduction

The estimated incidence of infective endocarditis (IE) in the general population varies depending upon the study, ranging from 16 to 62 cases per million person-years [1–3]. The disease carries high morbidity and mortality, which can reach 25% [4].

Advances in antibiotic therapy and refined surgical techniques have improved life expectancy for patients with IE. At the same time, diagnostic methods have become increasingly accurate and enable earlier diagnosis.

The indication for surgery is based on the presence of congestive heart failure, new onset of valvular regurgitation, persistent fever or bacteremia, systemic embolization, or large vegetations that imply a risk of embolization [5–9].

Whereas mitral valve repair is preferred over mitral valve replacement for degenerative disease, it remains unclear whether the same is true for IE [10, 11]. In the setting of IE, mitral valve repair may not be feasible, since the primary goal is to resect infected tissue, thus potentially precluding repair. Moreover, concerns have been raised regarding the durability of complex mitral valve repair, particularly when performed on extensively infected tissue (infection of the annulus and/or multiple leaflet segments). Several studies have suggested better survival after mitral valve repair than after mitral valve replacement in patients undergoing surgery for IE [12, 13]. However, most of these studies have a limited number of patients and were performed at a single center.

The members of The GAMEs Study Group are listed in Acknowledgements.

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The current study reports the results of a multicenter study on mitral valve repair for IE and compares them with those for replacement. If the frequency of relapse is not higher in the repair group, replacement could be extended to more patients, thus limiting the long-term complications of prosthetic valves.

Methods

Study design

This study is based on data from a Spanish nationwide prospective registry that included patients operated on for native mitral valve IE. The collaborating institutions pooled their data into the database of the Spanish GAMES group [Grupo de Apoyo al Manejo de la EndocarditiS (Group for support and management of infective endocarditis)]. Pre-, peri-, and postoperative and 1-year follow-up data were collected and analyzed (Table 1). IE was defined according to the Duke criteria [14] .

Mitral valve conditions and mitral repair techniques are described (Table 2).

Relapse was defined as reoccurrence of IE on the repaired mitral valve during the follow-up period. Recurrence was defined as identification of the same microorganism.

Only cardiac mortality was included. In-hospital mortality was defined as death during hospital stay or during the 30 days after surgery.

Table 1 Hospitalary differences, comorbidities, clinical course and etiology

Hospital expertise	Repair (68)	Replacement (301)	*p*
>400 major surgeries	19.7%	12.6%	0.113
Intraoperative TEE	18.3%	3.8%	0.075
Comorbidities–EuroSCORE			
Renal failure	10 (14.7%)	52 (17.3%)	0.609
Age	61 (46–70)	63 (53–73)	0.113
Sex (male)	52 (76.5%)	211 (70.3%)	0.312
Pulmonary disease	6 (8.8%)	57 (18.9%)	0.068
Coronary disease	12 (17.9%)	52 (17.3%)	0.282
AF	6 (8.8%)	56 (18.6%)	0.126
Hypertension	28 (41.2%)	148 (49.2%)	0.418
Peripheral vasc disease	5 (7.5%)	23 (7.7%)	0.892
EuroSCORE	9 (13.2)	53 (17.6)	0.489
Clínical course–etiology			
Nosocomial	9 (13,2%)	53 (17.6%)	0.489
Fever	54 (79.4%)	245 (81.3%)	0.837
Vascular phenomena	5 (7.3%)	43 (14.2%)	0.184
Embolisms	20 (29.4%)	99 (32.9%)	0.591
New murmur onset	42 (61.7%)	157 (52.1%)	0.193
Cardiac failure	28 (46.7%)	169 (57.1%)	0.138
Reactive chain protein (mean/IQR)	19 (6–86)	24 (7–89)	0.634
Persistent bactaeremia	4 (5.8%)	30 (9.9%)	0.412
Neurological events	11 (16.1%)	61 (20.2%)	0.549
Mechanical ventilation	6 (8.8%)	48 (15.9%)	0.189
Septic shock	8 (11.7%)	39 (12.9%)	0.948
Etiology (%)			
CoN *Staphylococcus*	4 (5.9%)	27 (9.0%)	0.407
S. aureus	14 (20.6%)	67 (22.3%)	0.764
Enterococcus sp.	11 (16.2%)	35 (11.6%)	0.305
Streptococcus sp.	26 (38.2%)	116 (38.5%)	0.963
Unknown	4 (5.9%)	20 (6.6%)	0.818
Urgent surgery	9 (13.2%)	81 (26.9%)	0.026
Preoperative hospital stay (days)	36 (27–61)	41 (28–57)	0.582

AF atrial fibrillation, *CoN* coagulase negative, *IQR* interquartile range, *TEE* transesophageal echocardiography

Table 2 Mitral valve condition

Mitral valve condition	Repair (68)	Replacement (301)	*p*
TEE performed	55 (80.9%)	258 (86.0%)	0.285
Vegetations observed	51 (75.0%)	254 (84.4%)	0.065
Perforation	33 (48,5%)	102 (33.8%)	0.033
Pseudoaneurysm	5 (7.4%)	27 (9.0%)	0.812
Abscess	9 (13.2%)	47 (15.7%)	0.782
Intracardiac fistulae	2 (2.9%)	5 (1.7%)	0.701
Normal ejection fraction	57 (83.8%)	259 (86.0%)	0.779
Mitral valve repair group			
Multiple valve surgery	24 (35.2%)		
Posterior leaflet infection	39 (57.3%)		
Anterior leaflet infection	31 (45.5%)		
Bileaflet extension	12 (17.6%)		
Ring infection	14 (20.5%)		
Pericardial tissue use	15 (22.0%)		
Annuloplasty performed	44 (64.7%)		

Mitral repair techniques

TEE transesophageal echocardiography

Table 3 Multivariate analysis of 1-year mortality

Variables	RR	95% CI	*p*
Renal failure	2.204	1.237–3.925	0.007
Septic shock	2.904	1.302–6.474	0.009
Nosocomial	3.617	1.789–7.309	0.000
Mitral valve repair	0.455	0.193–1.071	0.071
Age > 75	3.819	1.779–8.198	0.001
Cardiac failure	1.971	1.159–3.809	0.030
EuroSCORE > 15	2.101	1.159–3.809	0.014

Variables tested: hyperlipidemia, diabetes, *Streptococcus*, mechanical ventilation at surgery, hypertension, sex, cardiac arrest, communitary acquisition, atrio-ventricular block, mitral vegetation > 1 cm, abscess, vasopressive support prior to surgery, intra-aortic balloon of counterpulsation, antibiotics less than 29 days, renal failure, septic shock, nosocomial, mitral valve repair, age, cardiac failure, EuroSCORE, urgent surgery

Patients diagnosed between January 1, 2008 and July 31, 2016 in 27 Spanish hospitals ($n = 3524$) were reviewed. Only those patients with IE on the native mitral valve were selected, and those with previously implanted prostheses were excluded ($n = 1128$). Of the 1128 patients with IE on the native mitral valve, 437 underwent surgery. Finally, 369 patients completed the 1-year follow-up. The regional and local ethics committees approved the study, and patients gave their informed consent to be included in the database.

Predisposing conditions for IE were registered, including previous valve disease, previous valve replacement, and presence of intracardiac devices. Mortality during hospitalization and follow-up and in-hospital complications were also recorded. Recurrence, relapse, surgical reintervention, and death during follow-up were registered. Relapse and recurrence were defined as new IE on the repaired mitral valve. Valve-related morbidity was also addressed by registering valve deterioration (including structural and non-structural) and anticoagulation issues. Valve deterioration was considered with at least mild-to-moderate mitral insufficiency or stenosis after mitral valve repair or in the prosthetic valve. Valve thrombosis and valve deterioration were defined by local echocardiographists. Bleeding was considered positive if transfusion was needed.

Differences between hospitals regarding the number of operations and mitral repairs were analyzed.

Statistical analysis

Differences between groups were compared with the χ^2 test or Fisher´s exact test, as appropriate. Means and standard deviations were computed for continuous variables, and proportions were compared with the nonparametric Mann–Whitney *U* test or Student's test, as appropriate. Demographic variables were used to compare patients who underwent mitral valve repair with those who underwent mitral valve replacement. The long-term analysis of these groups was performed for the end points of mortality, recurrence of IE, and reoperation using Kaplan–Meier curves.

Late survival and time-dependent events were assessed by Kaplan–Meier survival analysis, and the log-rank test was used for univariate analysis.

The theoretical basis of propensity score analysis aims to create matched pairs or matched sets that are balanced with respect to many observed covariates [15]. The resulting matched sets are heterogeneous within the covariates, but the covariates aim to have uniform distributions in treated and control groups, which makes the groups as a whole comparable.

Propensity score analysis was carried out in our study to estimate the probability that a patient might undergo repair or replacement of the mitral valve and to eliminate the effect of nonrandomization and selection vias. A logistic regression analysis of several preoperative variables was performed to generate a single propensity score for each patient. Variables included were those differentially distributed among groups in the univariate analysis and published to be relevant regarding mitral valve repair (Table 3). The model had an area under the receiver operating characteristic curve of 0.677 and a Hosmer–Lemeshow goodness of fit *p* value of 0.431. Then, a subset analysis was used, in which patients were grouped according to their propensity score into five quintiles (Table 4), after which their characteristics and outcomes were compared within these quintiles. Groups with similar propensity scores appeared to be reasonably well matched with respect to all characteristics. Differences

Table 4 Number of patients matched according to the propensity score

Quintiles	Repair (68)	Replacement (301)	*p*
Quintile 1	6 (8.1)	68 (22.6)	0.058
Quintile 2	9 (12.2)	65 (21.6)	0.549
Quintile 3	10 (13.5)	64 (21.3)	0.651
Quintile 4	18 (24.3)	56 (18.6)	0.774
Quintile 5	25 (34.2)	48 (15.9)	0.238

Variables included: concomitant surgery, cardiogenic shock, renal failure, septic shock, nosocomial acquisition, age, EuroSCORE, high volume centers, atrial fibrillation, mechanical ventilation at surgery, *S. aureus*, urgent surgery

with a p value less than 0.05 were considered statistically significant.

Risk score was calculated using EuroSCORE I.

Results

Baseline characteristics

Of the more than 3000 cases of IE, 1513 were selected as specific mitral valve endocarditis. Prosthetic valve endocarditis was excluded, leaving a final cohort of 1128 patients. Of these, 437 finally underwent surgery. Only 38.7% (437/1128) of the patients with proven IE underwent surgery. The remaining patients were managed conservatively or considered to be at high risk. After excluding patients with double valve surgery and incomplete follow-up, the final cohort comprised 369 who had undergone surgery for native mitral valve IE (Fig. 1). A total of 68 patients (18.4%) underwent valve repair, and 301 underwent valve replacement.

Comparison between repair and replacement

Both cohorts were analyzed before comparing mortality between them. Both groups were compared in terms of hospital experience, comorbidities, clinical course, etiology, echocardiographic features, preoperative risk profile (EuroSCORE), and surgery.

For surgical expertise and number of major operations and mitral valve repairs performed in Spain, we decided to establish a cutoff point of 400 operations and 50 cases of mitral valve repair per year. We also analyzed the impact of having transesophageal echocardiography (TEE) in the operating room. The repair rate was higher in hospitals performing more mitral valve repairs (19.7% vs 12.6%; p = ns) and having TEE probes in the operating room (18.2% vs 3.8%; p = ns) (Table 1).

Both groups were comparable with respect to comorbidities (Table 1). Age, sex, and other confounding factors were distributed similarly between the repair and the replacement groups.

Few differences were observed in the clinical course of IE (Table 1). Place of acquisition, fever, peripheral embolic phenomena, and laboratory data on the infection were equally distributed in both groups. The valve was replaced in patients with cardiogenic shock and patients undergoing emergency surgery.

For mitral valve conditions, two main differences were observed (Table 2). The presence of perforations was clearly correlated with an increased rate of valve repair. Conversely, the presence of abscesses was correlated with mitral valve replacement. Regarding mitral valve conditions in the repair group, only 17.6% of the patients had both leaflets affected (anterior and posterior). Pericardial patches were used in 22.0% of the cases. Annuloplasty rings were implanted in 64.7%. Only 35.2% of the patients underwent multiple valve surgery.

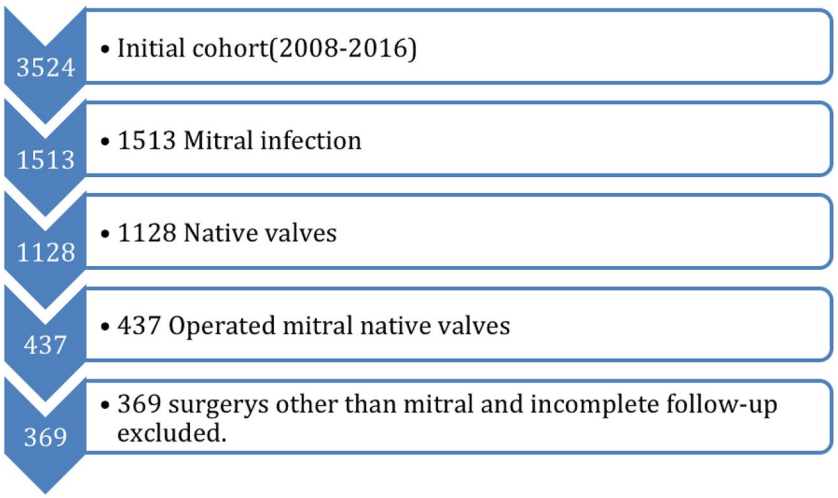

Fig. 1 Population distribution

Due to the high variability in hospitals and surgeons, it is difficult to make conclusions regarding valve reparability. However, it could be noted that more pericardial tissue use could eventually permit reaching higher repair rates. Repair groups are not affected by anterior or posterior leaflet infection, thus reflecting that probably repair rates should increase globally in Spain. Hospital expertise leads to higher repair rates globally, and in the endocarditis subset also.

No differences were observed for other clinical aspects, including the Duke criteria or etiologic agent. Aggressive pathogens such as *Staphylococcus aureus* did not affect repair or replacement rates. Even when IE was due to bacteria considered "very aggressive" (*S. aureus*), it did not indicate the need for mitral valve replacement.

In-hospital mortality

Eleven patients died in the repair group (16.2%) and 82 died in the replacement group (27.2%) ($p=0.058$) (Table 5). As there were slight EuroSCORE differences between the groups, the decision was made to analyze differences in mortality using risk-adjusted mortality, which results from dividing observed mortality by expected mortality (as expressed in the EuroSCORE). Both groups can then be standardized. Risk-adjusted mortality was 2.16 in the repair group and 3.48 in the replacement group.

Mean (range) hospital stay (Table 1) did not differ between the groups (repair 36 days [27–61]; replacement: 41 days [28–57]; $p=0.522$).

For in-hospital morbidity, no differences were found between the groups, which had similar rates of surgical complications, except for the surgical site infection rate, which was slightly higher in the replacement group ($p=0.067$).

Table 5 Morbidity and mortality after 1 year follow-up

Outcome	Repair $n=68$ (%)	Replacement $n=301$ (%)	p
In-hospital mortality	11 (16.2)	82 (27.2)	0.058
One year mortality	2 (2.9)	11 (3.7)	0.773
Global mortality	13 (19.1)	93 (30.9)	0.053
Recidives	2 (2.9)	7 (2.3)	0.890
Re-intervention at f-u	2 (2.9)	15 (4.9)	0.685
No complication at f-u	52 (76.5)	192 (63.8)	0.046
Valve-related/OAC morbidity			
Valve deterioration	11 (16.2)	43 (14.3)	0.834
Thrombosis	0	14 (4.6)	0.143
Embolism	2 (2.9)	31 (10.3)	0.092
Bleeding	2 (2.9)	74 (24.6)	0.001

Valve deterioration: includes structural and non-structural deterioration

f-u follow-up, *OAC* oral anticoagulation therapy

Follow-up

The primary end point was mortality. The two secondary end points were cardiac-related reintervention or relapse of IE.

Two deaths occurred in the repair group at 1 year (2/57: 3.5%). Eleven patients died in the replacement group (11/222: 4.9%). However, this difference was not statistically significant (3.5% vs 4.9%; $p=0.476$).

Reinterventions were more frequent in the replacement group (15/219:6.8%) than in the repair (2/57 := 3.5%) group (6.8% vs 3.5%, $p=0.531$).

Two relapses occurred in the repair group (2.9%) and 7 in the replacement group (2.3%). This difference was not significant ($p=0.890$). Interestingly, of all these relapses (9), only 1 was caused by the same microorganism (*Enterococcus faecalis*) and affected a patient in the valve replacement group.

The Kaplan–Meier analysis (Fig. 2) revealed a clear tendency toward better survival in the repair group after 100 days of follow-up. Although the difference was not statistically significant ($p=0.064$)—probably owing to the low number of patients—survival seems to be better when the mitral valve is repaired.

We created a composite end point to highlight these differences. We analyzed the number of patients alive after 1 year without having had reinfection or having needed resurgery. At 1 year, 76.5% of the patients from the repair group had no complications and were considered "cured". This percentage was 63.8% in the replacement group ($p=0.046$) (Table 5).

Valve deterioration, thromboembolism and bleeding were also recorded and the results obtained (Table 5) highlight benefits from mitral valve repair. Valve deterioration was considered positive with at least mild regurgitation or stenosis. No differences were observed regarding this feature probably because of the short-term follow-up and the definition used (mild-to-moderate mitral insufficiency was considered valve deterioration). However, thrombosis, embolism and bleeding tend to be related to mitral valve replacement with a tendency to statistical signification. Although a sideline end point, these morbidity results emphasize the benefits of mitral valve repair.

When the variables considered to be significant in the univariate analysis were entered into the model, repair tended to be significant (OR 0.455; 95% CI 0.193–1.071; $p=0.071$); however, it lost power when compared with other factors such as renal failure, septic shock, nosocomial infection, age above 75 years, high EuroSCORE, and cardiac failure (Table 3).

Of note, 7 patients experienced a relapse of IE, but did not undergo surgery and had not died when the event was censored. In addition, 7 patients were considered healed in

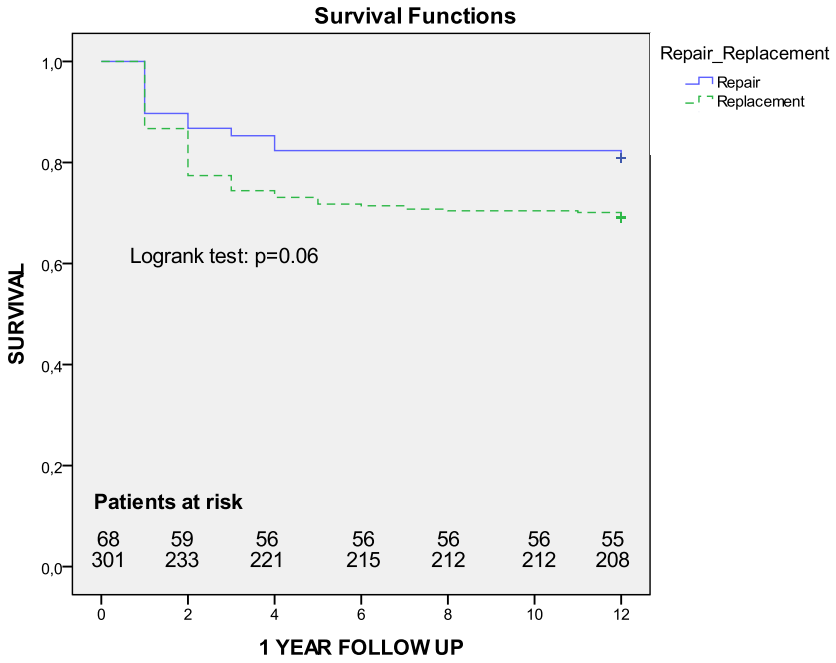

Fig. 2 Survival after 1 year of follow-up

microbiological terms, but needed cardiac surgery owing to other problems.

Discussion

Mitral valve IE remains a challenging condition requiring a multidisciplinary approach, as accepted in current guidelines [16].

In certain cases, the lack of tissue precludes valve repair. However, a sufficient amount of tissue can sometimes be preserved to enable repair, without compromising the idea that all infected tissue should be resected [17]. If the extension of the infection reaches the annulus, or abscesses are observed, repair is certainly more difficult as it can be observed in our results. Although rarely used in our series (22.0%), the use of pericardial patches has proven efficacy and can help permit the repair of the valve [18], particularly if perforations are observed. There is still some surgical concern and valves tend to be replaced in certain cases even when repair is feasible [19]. Real-world situations differ from high-experience center results [20, 21]. This nationwide study was mainly designed to confirm the idea that mitral valve repair is not inferior to replacement in terms of relapse or heart-related reinterventions [22]. In spite of the relatively low repair rate achieved in this study as compared to other series [20, 23, 24], clinical advantages are observed when repairing the infected valve. This should encourage surgeons to obtain experience in new techniques to gain reparability skills. Valve repairability and clinical results across the country in a real-world scenario are key points in this study.

With respect to valve reparability: differences between groups could be interpreted as factors predisposing to mitral valve repair. The possibility of repair decreases as the severity of the infection increases and the health status of the patient worsens. In our study, the EuroSCORE and other important measures of comorbidity did not differ between the groups, so that certain conclusions can be drawn with respect to valve reparability. First, departmental experience and surgical expertise confirm to be clearly related to the possibility of repair. Consequently, transferring stable patients to reference centers could be justified [16]. Elective surgery is the best option, with patients being under appropriate microbiological treatment and stable hemodynamic conditions. Care must be taken not to misunderstand elective and delayed, as it has been proven that early surgery leads to better results [21]. As we can observe, urgent surgery leads to lower repair ratios with statistical significance. As a matter of fact, timing is crucial when deciding to operate on these patients and it is still under debate. Anterior leaflet infection does not seem to preclude mitral valve repair. On the contrary, repair expertise in the surgical team seems to be crucial. On behalf of these results, the advice would be to reach higher repair rates in endocarditis cases through a global reparative approach to mitral patients. In addition to elective surgery in reference centers, our results reinforce the idea of multidisciplinary team assessment for imaging and management of antibiotics.

Mortality appears to be higher if the valve is finally replaced, regardless of the patient's individual risk (Table 3). In other words, mitral valve repair has a statistical significance toward being protective. Other variables are linked to

mortality at 1 year: renal failure, septic shock, nosocomial acquisition, age > 75 years, cardiac failure and EuroSCORE > 15. At 1 year, mortality is higher in the replacement group and the rates of relapse and reintervention can be used as a composite end point showing that if a patient is finally included in the repair group, prognosis should be better. Risk-adjusted mortality results seem to indicate that valve replacement worsens prognosis at 1 year. These patients will also have to deal with the complications of the prosthesis and anticoagulation issues in the long term.

Conclusions

In addition to describing the current practice in mitral valve surgery for native endocarditis in Spain, this article attempts to shed light on the progress of patients depending on the surgical approach used to treat the infection. In terms of prognosis, this information may prove useful for patients and their families, as well as for the surgeon. Planning surgery is easier if the results of a complicated repair encourage the effort that has to be made to preserve the valve. Repair rates are low, but probably increase as the surgical community becomes more aware of these results and knowledge of mitral repair improves [20]. If the patient is stable, reference centers represent the best way of improving outcomes in such a complicated disease [20].

Our study is limited by its multicenter design, which necessarily implies a lack of homogeneity in surgical treatment. At the same time, longer follow-up with a larger cohort of patients could probably help in better understanding the role of mitral valve repair in patients with native mitral valve IE.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interest.

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