Women Undergoing Mitral Valve Replacement: A Retrospective Analysis
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Abstract

Background: Although cardiovascular disease is the leading cause of death in women, few data exist on risk factors and treatment of these diseases in women. This leads to a delay in the institution of appropriate therapies and worse outcomes in this population.

Objective: We aimed to identify predictors of morbidity and mortality in women undergoing isolated mitral valve replacement.

Methods: This was a retrospective cohort study with 104 women who underwent isolated mitral valve replacement at a referral hospital for treatment of cardiovascular diseases, performed from January 2011 to December 2016. Data were obtained from medical records. Statistical analysis was performed to calculate odds ratio, unpaired Student's t-test, and binary logistic regression. P values <0.05 were considered statistically significant.

Results: Mean age of patients was 43.73 (±13.85) years. Most patients had a diagnosis of rheumatic disease prior to surgery (76%; N=79). Mortality rate was 4.9% (N = 5). There was a statistically higher risk of death among patients with reduced ejection fraction (EF) (<50%) (OR = 14.833, 95% CI 2.183 - 100.778, P=0.001) and older age (P = 0.009). There was an inverse association between a previous diagnosis of rheumatic disease and death (OR = 0.064, 95% CI 0.007 - 0.606, P=0.002). Logistic regression showed reduced EF at preoperative evaluation as a predictor of death and a diagnosis of rheumatic disease as a protective factor.

Conclusion: Older age and reduced EF were associated with postoperative mortality. Reduced EF was a predictor of death, and rheumatic disease was associated with better surgical outcomes.

Keywords: Morbidity; Mortality; Thoracic Surgery; Mitral Valve; Women.

Introduction

Cardiovascular disease (CVD) is the leading cause of death in developed countries and, in Brazil, despite regional differences, CVD kills more than any other cause. CVD is also the leading cause of death among women, and usually occurs 7–10 years later than men. However, the prevalence of this disease increases in the postmenopausal period, possibly due to the decrease in estrogen hormone levels.

There are few data in the literature about the assessment of risk factors and treatment of CVDs in women, as compared to men, including in Brazil. This leads to a delay in the institution of appropriate therapies, so that women often receive less aggressive treatments and are less likely than their male counterparts to be managed following recommended guidelines.

Mitral valve disease is the most common valvular heart disease. In developing countries, the main cause of mitral valve stenosis is rheumatic fever, and mitral valve replacement is currently one of the most common
treatments for this condition. Mitral stenosis and regurgitation may cause pulmonary hypertension and right heart failure, leading to poor outcomes.

Sex differences in outcomes have been noted in many areas of cardiovascular medicine, and this is not different in mitral valve disease, although the causes of such differences are not well understood. Prior studies have hypothesized that differences in mitral valve morphology, complexity of lesions, timing of interventions, and comorbid conditions place female patients at a disadvantage at the time of surgery. Although women are as likely to have significant mitral valve disease, they are less likely to receive surgery than male patients and, when they do, operative mortality is higher among women undergoing mitral valve repair or replacement compared to men.

The purpose of this article was to identify preoperative, intraoperative, and postoperative risk factors for morbidity and mortality in a Brazilian female group of patients who underwent isolated mitral valve replacement, to obtain pertinent information regarding the current scenario in Brazil and contribute to a more gender-specific and individualized treatment of women.

Methods

This was a retrospective cohort study that analyzed the medical records of patients who underwent isolated mitral valve replacement at a referral center for treatment of cardiovascular diseases located in the city of Salvador (Bahia, Brazil). Primary outcome was death in the postoperative period of isolated mitral valve surgery, and secondary outcome was incidence of morbidity.

Female patients who underwent isolated mitral valve replacement between 2011 and 2016, regardless of age, valve lesion etiology, or type of prosthesis, were included. Patients who underwent mitral valve replacement in combination with any other surgical procedure were excluded. Patients with missing information and those whose medical records were not available were also excluded.

Of 207 patients, 43 were excluded due to lack of information in the medical records, leaving 164 patients. Of these, 60 male patients were excluded, remaining 104 female patients for analysis.

Clinical and laboratory data from the preoperative, intraoperative, and postoperative periods were collected from medical records, using a standardized form. Table 1 lists all variables and outcomes investigated.

### Statistical analysis

Statistical analysis was performed using the software IBM SPSS statistics for Windows, version 23.0. Categorical variables were presented as absolute and relative

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**Table 1 – Variables and outcomes evaluated in a sample of female patients (n=104) who underwent isolated mitral valve replacement between 2011 and 2016**

| 1. Age                                      |
| 2. Gender                                   |
| 3. Height                                   |
| 4. Weight                                   |
| 5. Body mass index                          |
| 6. NYHA functional classification           |

**7. Preoperative comorbidities:**

| a. Stroke                                   |
| b. Diabetes mellitus                        |
| c. Rheumatic fever                          |
| d. Endocarditis                             |
| f. Asthma                                    |
| g. Smoking                                  |
| h. Coronary artery disease                  |
| i. Atrial fibrillation (AF)                  |
| j. Chronic obstructive pulmonary disease    |
| k. Previous valve operation                 |
frequencies, whereas continuous variables were presented as means and standard deviations. Associations between categorical variables were assessed by odds ratio (OR). The Kolmogorov-Smirnov test was used to evaluate the normality of data distribution. Means were compared using the unpaired Student’s t-test.

Binary logistic regression was used to identify possible predictors of postoperative death, using Nagelkerke’s coefficient of determination ($R^2$). P-values <0.05 were considered statistically significant.

**Ethical considerations**

This study was approved by the Research Ethics Committee of the Ana Nery Hospital (protocol no. 336.981, approved on July 19, 2013). In accordance with Resolution No. 466/2012 of the Brazilian National Commission for
Research Ethics on research involving human beings, this study protocol was registered on the Plataforma Brasil website (CAAE number 14268813.5.0000.0045). The authors signed a form to assure that patient data would be kept confidential. The standardized form used to collect patient information was approved by the local institutional review board.

**Results**

Mean age of the sample was 43.73 (±13.85) years. Mean body weight was 61.38 (±12.02) kg, and mean body mass index was 24.44 (±4.46) kg/m². Thirty patients (28.8%) had no record of medication use, while 74 (71.2%) were on drug therapy, mostly diuretics (N=54; 51.9%) and betablockers (N=49; 47.1%). Nineteen patients (18.3%) had received penicillin. Preoperative evaluations indicated that 95.2% of the patients had at least one comorbidity, and most of them (N=79; 76%) had been diagnosed with rheumatic heart disease prior to surgery (Table 2).

Mitrail repair had been performed in 18 (17.3%) patients and 9 (8.6%) had been submitted to mitral valve replacement. The mean European System for Cardiac Operative Risk Evaluation score (EuroSCORE) was 5.11 (±7.45). Laboratory test results prior to the mitral valve surgery are described in Table 3.

Most patients had sinus rhythm on preoperative electrocardiogram (N=48; 46.2%), with no other changes described. Thirty-five patients (33.7%) had atrial fibrillation (AF), one had (1.0%) atrial flutter, four (3.8%) had bradycardia, and three (2.9%) had tachycardia. Three patients (2.9%) had other cardiac alterations.

The most commonly reported valve dysfunction was mixed mitral valve lesions (N=43; 41.3%), followed by mitral valve regurgitation (N=38; 36.5%) and stenosis (N=15; 14.4%) (Figure 1). The most common valvular lesion was tricuspid regurgitation, found in 68 (65.4%) patients. In patients with valvular prosthesis, regurgitation (N=7; 77.8%) and mixed lesions (N=2; 22.2%) were observed.

Of the total number of patients, only one patient underwent urgent surgery. Biological prostheses were the most used prosthetic heart valves (N=72; 69.2%); the most common size of the prosthesis was 29 mm (N=49; 47.1%), followed by 31 mm (N=30; 28.8%) and 27 mm (N=9; 8.7%). Papillary muscle and chordae tendineae were preserved in all patients, whenever technically possible.

| Comorbidities                        | Frequency  |
|--------------------------------------|------------|
| Rheumatic disease                    | 79 (76.0%) |
| Hypertension                         | 39 (37.5%) |
| Atrial fibrillation                  | 36 (34.6%) |
| Smoking or former smoking            | 15 (14.4%) |
| Stroke                               | 16 (15.4%) |
| Endocarditis                         | 10 (9.6%)  |
| Diabetes mellitus                    | 12 (11.5%) |
| Asthma                               | 5 (4.8%)   |
| Coronary artery disease              | 4 (3.8%)   |
| Chronic obstructive pulmonary disease| 1 (1.0%)   |

| NYHA functional class | Frequency |
|-----------------------|-----------|
| 1                     | 2 (2.2%)  |
| 2                     | 44 (47.3%)|
| 3                     | 36 (38.7%)|
| 4                     | 11 (11.8%)|

*NYHA: New York Heart Association*
possible. Prophylactic anticoagulation therapy for postoperative thrombosis was made immediately after drain removal.

The overall mortality rate was 4.9% (N=5), with sepsis as the leading cause of death (N=2; 40.0%), followed by tachyarrhythmia (N=1; 20.0%). One death was registered due to Chagasic cardiomyopathy (20%), and in one case, no specific cause of death was recorded. Three of the five patients who died had low left ventricular ejection fraction (LVEF) before surgery.

The mean number of days the patients stayed in the intensive care unit was 5.24 (± 4.47) days, with a mean length of stay of four days.

The most common postoperative complications were arrhythmias (N=24; 23.1%), followed by respiratory tract infection (N=14; 13.5%) and renal failure (N=8; 7.7%) (Table 4). The most common arrhythmia was AF (N=18; 75.0%), followed by supraventricular tachycardia (N=2; 8.3%) and ventricular tachycardia (N=2; 8.3%). One case of atrial flutter and one of complete heart blockage were reported (4.2% for each).

Comparing the mean age of patients who died after surgery with those who survived, a statistically significant difference was observed, indicating that older age was associated with the primary outcome (Table 5). Low LVEF (< 50%) was associated with the risk of death in the postoperative period.

A previous diagnosis of rheumatic disease was associated with a reduced risk of postoperative mortality. However, these patients were significantly younger than those who did not receive this diagnosis (40.4 years vs. 54.2 years; P<0.001).

The presence of arrhythmias in the preoperative period was not associated with mortality after valve replacement (Table 6). The same was observed for patients with a previous diagnosis of hypertension, endocarditis, or stroke. Since no patient with diabetes, coronary artery disease, obesity (BMI > 30 kg/m²), chronic obstructive pulmonary disease (COPD), or asthma died, it was impossible to establish associations of these variables with the primary outcome.

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**Table 3 - Preoperative laboratory results of women undergoing isolated mitral valve replacement (n=104)**

| Exams                              | Mean (standard deviation) | Frequencies |
|------------------------------------|---------------------------|-------------|
| Hemoglobin (g/dL)                  | 12.09 (± 1.69)            | -           |
| Hematocrit (%)                     | 36.26 (± 5.50)            | -           |
| Creatinine (mg/dL)                 | 1.06 (± 0.73)             | -           |
| Urea (mg/dL)                       | 34.47 (± 24.74)           | -           |
| International Normalized Ratio     | 1.43 (± 0.57)             | -           |
| Prothrombin time (%)               | 73.06 (± 26.31)           | -           |
| Left atrium (mm)                   | 52.95 (± 16.24)           | -           |
| Aorta (mm)                         | 28.66 (± 5.56)            | -           |
| LV systolic diameter (mm)          | 33.73 (± 8.66)            | -           |
| LV diastolic diameter (mm)         | 51.88 (± 9.28)            | -           |
| Posterior wall thickness (mm)      | 8.11 (± 1.86)             | -           |
| Interventricular septum (mm)       | 8.13 (± 1.83)             | -           |
| LV ejection fraction (%)           | 63.07 (± 10.86)           | -           |
| Pulmonary artery systolic pressure (mmHg) | 48.75 (± 18.31) | - |
| Calcification                       | -                         | 29 (27.9%)  |
| Paravalvular leak                  | -                         | 11 (10.6%)  |

*LV: Left ventricular*
The New York Heart Association (NYHA) functional classes III/IV, previous mitral valve surgery, and type of heart valve disease were also not associated with higher mortality.

All variables that showed an association with mortality were submitted to multivariate analysis by binary logistic regression. A significant model was obtained with reduced LVEF (< 50%) and prior diagnosis of rheumatic disease as variable ($\chi^2 (2) = 14.262, P = 0.001; R^2$ Nagelkerke = 0.402) (Table 7). The same did not happen for age.

Reduced ejection fraction was a predictor of postoperative death in the model, and a prior diagnosis of rheumatic disease was associated with better surgical outcomes.

**Discussion**

Rheumatic disease was the most frequent comorbidity in our sample. This was expected, since in underdeveloped and developing countries like Brazil, this disease remains endemic, and is the main etiology of valve dysfunction. In addition, it is known that its prevalence is higher in the female population, which has been confirmed by most studies on valve disease.

As observed in the present study, mean age of patients undergoing valve replacement due to rheumatic etiology is relatively low, in accordance with previous
On the other hand, participants of studies carried out in high-income countries are older, due to the predominance of degenerative and ischemic etiology of valve disease.10,19 Studies have shown that mortality of cardiac surgery among women is higher than of their male counterparts,3,5,6,11,20-22 since women receive surgery late and usually have more severe preoperative conditions.3,6,11,21,23 One of the possibilities for this fact is the use of cutoff points for echocardiographic variables without considering their body mass, which is generally lower than men’s. Others have postulated about the differences in symptom manifestation, anatomical or even pathophysiological features. In this study, however, mortality rate was within normal range (4 to 7%),24 similarly to previous reports.10,19,25

There is considerable controversy about the risk factors associated with mortality after valve replacement surgery. Results have varied widely according to the population and the study method. Age, for example, has already been associated with higher mortality in several studies, as well as in ours.3,10,12,16,22,28-31 However, this is still not a consensus, since others have found no difference between groups,25,32 or even an inverse relationship.19,23,33

There are no records of the influence of rheumatic disease on postoperative outcomes. Khan et al.17 showed a correlation between high levels of anti-streptolysin O and mortality. However, this is a marker of the acute phase of rheumatic fever, rather than its sequel. We found in this study that a history of rheumatic disease was a protective factor, associated with lower immediate mortality. We emphasize, studies.12,15,17

| Table 4 – Postoperative outcomes of women undergoing isolated mitral valve replacement (n=104) |
|---------------------------------------------------------------|
| **Outcomes** | **Frequencies** |
| Arrhythmias | 24 (23.1%) |
| Respiratory tract infection | 14 (13.5%) |
| Renal insufficiency | 8 (7.7%) |
| Death | 5 (4.9%) |
| Pericardial effusion | 3 (2.9%) |
| Surgical wound infection | 5 (4.8%) |
| Sepsis | 4 (3.8%) |
| Pleural effusion | 3 (2.9%) |
| Mediastinitis | 4 (3.8%) |
| Reoperation | 4 (3.8%) |
| Urinary tract infection | 3 (2.9%) |
| Cardiac tamponade | 1 (1.0%) |
| Endocarditis | 2 (1.9%) |
| Subcutaneous emphysema | 0 (0.0%) |
| Stroke | 0 (0.0%) |
| Pneumothorax | 0 (0.0%) |
| Acute heart failure | 0 (0.0%) |
| Pulmonary thromboembolism | 1 (1.0%) |
We did not find any relationship between any other preoperative variable (diagnoses or laboratory findings) and higher mortality, which is in line with results reported by Fernandes et al.\textsuperscript{28} and De Bacco et al.\textsuperscript{32} However, previous publications have reported an association of elevated BMI values,\textsuperscript{10,26} history of coronary artery disease,\textsuperscript{16,22,30,33} endocarditis,\textsuperscript{22} stroke\textsuperscript{30}, hypertension and COPD\textsuperscript{19} with postoperative complications and death. Among laboratory variables, elevations in creatinine / kidney injury\textsuperscript{17,19,22,32} and reduced hemoglobin and hematocrit values\textsuperscript{28} have already been reported as risk factors, which was not observed in this study.

| Variable                                      | N (%) | Deaths | Odds ratio | 95% confidence interval | p-value |
|-----------------------------------------------|-------|--------|------------|-------------------------|---------|
| Obesity (BMI > 30 kg/m2)                      | 11 (12.4%) | 0 (0.0%) | -          | -                       | 0.508   |
| Arrhythmias                                   | 46 (49.5%) | 4 (8.7%) | 4.381      | 0.471 - 40.778          | 0.160   |
| NYHA functional class III/IV                  | 47 (50.5%) | 2 (4.3%) | 0.978      | 0.132 - 7.250           | 0.982   |
| Stroke                                        | 16 (15.5%) | 1 (6.3%) | 1.383      | 0.144 - 13.247          | 0.777   |
| Rheumatic disease                             | 79 (76.7%) | 1 (1.3%) | 0.064      | 0.007 - 0.606           | 0.002   |
| Chronic obstructive pulmonary disease         | 1 (1.0%) | 0 (0.0%) | -          | -                       | 0.820   |
| Coronary artery disease                       | 4 (3.9%) | 0 (0.0%) | -          | -                       | 0.645   |
| Diabetes                                      | 12 (11.7%) | 0 (0.0%) | -          | -                       | 0.405   |
| Hypertension                                  | 39 (37.9%) | 2 (5.1%) | 1.099      | 0.175 - 6.887           | 0.920   |
| Asthma                                        | 5 (4.9%) | 0 (0.0%) | -          | -                       | 0.605   |
| Smoking                                       | 15 (14.6%) | 0 (0.0%) | -          | -                       | 0.344   |
| Atrial fibrillation                           | 36 (35.0%) | 2 (5.6%) | 1.255      | 0.200 - 7.877           | 0.808   |
| Endocarditis                                  | 9 (8.7%) | 1 (11.1%) | 2.813      | 0.280 - 28.264          | 0.361   |
| Previous valve surgery                        | 39 (37.9%) | 1 (2.6%) | 0.395      | 0.043 - 3.666           | 0.599   |
| Urgent surgery                                | 1 (1.0%) | 0 (0.0%) | -          | -                       | 0.839   |
| Mitral calcification                          | 29 (28.2%) | 1 (3.4%) | 0.625      | 0.067 - 5.840           | 0.678   |
| LV ejection fraction                          | 12 (11.7%) | 3 (25.0%) | 14.833     | 2.183 - 100.778         | 0.001   |
| Mitral regurgitation                          | 37 (35.9%) | 3 (8.1%) | 2.824      | 0.450 - 17.724          | 0.250   |
| Mitral stenosis                               | 15 (14.6%) | 0 (0.0%) | -          | -                       | 0.344   |
| Mixed mitral lesion                           | 43 (41.7%) | 2 (4.7%) | 0.927      | 0.148 - 5.799           | 0.935   |
| Lesions in other valves                       | 81 (79.4%) | 5 (6.2%) | -          | -                       | 0.243   |
| Paravalvular leak                             | 10 (9.7%) | 0 (0.0%) | -          | -                       | 0.452   |

BMI: Body Mass Index; NYHA: New York Heart Association; LV: Left Ventricular
Table 7 – Predicting variables of postoperative death

| Variable               | B     | Significance | OR     | 95% CI to OR |
|------------------------|-------|--------------|--------|--------------|
|                        |       |              |        | Inferior     | Superior    |
| χ²(2) = 14.262, P = 0.001 |       |              |        |              |             |
| Low ejection fraction  | 2.795 | 0.012        | 16.367 | 1.860        | 144.024     |
| Rheumatic disease      | -2.832| 0.022        | 0.059  | 0.005        | 0.660       |
| Constant               | 2.458 | 0.027        | -      | -            | -           |

R²: determination coefficient; χ²: chi square; CI: confidence interval; OR: Odds ratio
The severity of symptoms according to the NYHA functional classification was not related to worse outcomes, which is in accordance with the study by De Bacco et al. This contrasts with most previous studies, although none of them had a similar sample to ours, i.e., with a predominance of females and rheumatic disease as the main etiology of the disease.

As previously found, lower LVEF was associated with higher mortality. This result is understandable, given that patients with impaired cardiac function tend to have more complications in the postoperative period. However, other echocardiographic variables did not show a correlation with worse outcomes, as previously described.

In our study, characteristics related to surgery, such as urgency, type of valve prosthesis, type of valve disease, or cardiopulmonary bypass and aortic clamping times did not show any influence on mortality. Among these, while some studies have suggested the use of bioprosthesis as a risk factor, several others have not observed worse outcomes with its use, as we have seen in the present study. It is noteworthy that biological valves have been more frequently used than mechanical ones. The latter require anticoagulation for life, with strict control of INR, and consequently require access to health services and good treatment adherence. Unfortunately, the patients of our sample would probably have difficulty accessing health care after surgery. Thus, probably, the choice of the type of prosthesis was based not only on technical but also on socioeconomic issues, and the decision was made by the medical staff and the patient.

Kim et al. and Cruz et al. have demonstrated severe tricuspid regurgitation as a risk factor, and Rankin et al. and De Bacco et al., respectively, have identified a history of previous valve surgery, and urgency of surgery as risk factors. Elevated cardiopulmonary bypass and aortic clamping times have already been described by Bueno et al. However, we could not demonstrate such associations, which is in accordance with results reported in other studies.

We found a long average intensive care unit stay (5.34 days). This can be explained by the discharge protocol, in addition to the occurrence of complications such as acute renal failure, reoperations and infections, as seen in Table 4.

As limitations, it is worth mentioning that the study is retrospective and was performed at a single center. Data were obtained from medical records and the results may have been influenced by problems in data recording. Our sample had a limited number of patients, which may have prevented detection of statistical significance in some situations. For those reasons, we must have caution in making population inferences. It is also good to remember that Brazil is a heterogeneous country, and the study was performed in a single location, where rheumatic disease is still endemic and responsible for most of the cases referred to surgery for mitral disease. These results should not be extrapolated to other regions.

Conclusion

Advanced age and reduced LVEF at preoperative evaluation were associated with a greater risk of mortality in women undergoing isolated mitral valve replacement. Rheumatic disease was associated with better surgical outcomes.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital Ana Nery under the protocol number 336.981. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Author contributions

Conception and design of the research: Baucia JA, Moreira JL. Acquisition of data: Moreira JL. Analysis and interpretation of the data: Barletta PH, Moreira JL. Statistical analysis: Barletta PH. Writing of the manuscript: Baucia JA, Moreira JL, Barletta PH. Critical revision of the manuscript for intellectual content: Moreira, JL.
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