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# Prognostics of Feasibility of Mitral Valve Ring Annuloplasty for Moderate Functional Mitral Regurgitation Associated with Severe Aortic Valve Disease

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## ABSTRACT

**Background:** Management of moderate functional mitral regurgitation (FMR) commonly accompanying severe aortic valve (AV) disease is still debatable without specific guidelines. Prognostics accused of postoperative residual mitral regurgitation (MR) in either severe aortic stenosis (AS) or regurgitation (AR) patients are unclear and still questionable.

**Objective:** This study was aimed to identify the preoperative predictors of residual MR in patients with severe AS or AR and moderate FMR subjected to aortic valve replacement (AVR) with or without mitral valve (MV) ring annuloplasty repair.

**Patients and Methods:** This retrospective comparative study involved 87 patients presented with severe AS or AR associated with moderate FMR. Patients were divided into two groups **Group (I)** that included 40 patients who were subjected to AVR only and **Group (II)** that included 47 patients who were subjected to AVR and MV ring annuloplasty repair.

**Results:** Significant predictors of overall mortality were atrial fibrillation (AF) ($p$=0.011) and residual MR ($p$=0.001), of early residual MR were unattempting MV repair ($p$=0.007) and prolonged inotropic support ($p$=0.015), of late residual MR were postoperative FMR grade 2 or more ($p$=0.008), persistent AF ($p$=0.046) and left atrial diameter (LAD) >5 cm ($p$=0.054), and of development of residual MR among AS populations were AF ($p$=0.01), LAD >5 cm ($p$=0.002), peak AV gradient <60 mmHg ($p$=0.01) and mean AV gradient <40 mmHg ($p$=0.02) while left ventricular end-systolic diameter (LVESD) <4.5 cm ($p$=0.001) for AR patients.

**Conclusion:** It could be concluded that the preoperative grade 2 FMR per se is not associated with poor overall survival rate and is not an independent risk factor for postoperative mortality for either AS or AR patients. The postoperative residual MR with its congestive heart failure lethal sequelae is strongly associated with postoperative complications and higher overall mortality. We strongly recommend combined MV ring annuloplasty during AVR when there are any of the forementioned preoperative risk factors.

**Keywords:** FMR, Secondary Mitral Regurgitation, AV disease, MV ring annuloplasty, AVR.

## INTRODUCTION

Functional or secondary mitral regurgitation (FMR) is a common surgical entity that is frequently met with severe aortic valve (AV) disease whether aortic stenosis (AS) or regurgitation (AR). Its incidence with such pathologies that eventually need aortic valve replacement (AVR) to be cured reaches as high as 75% [(1,2)].

FMR is clearly demonstrated when the mitral valve (MV) leaflets are incompetent allowing backward flow of blood from the left ventricle (LV) to the left atrium (LA) during systole although the MV apparatus doesn't show significant structural nor intrinsic valvular pathology [(2)]. Its common association with severe AV disease is assumed to the LV geometric changes. LV hypertrophy, LV dilatation or MV annular dilatation would result in variable degrees of FMR [(3)].

Management of the moderate degree of FMR commonly associated with severe AV disease is still debatable and no specific guidelines are illustrated despite its high frequency [(3)]. Moreover, dealing with it in the surgical setting whether to repair the MV annulus or not is generally and largely dependent on the operator's preference based on some reports that claimed improvement of almost 50% of the FMR cases without surgical intervention. However, most of these reports involved patients with ischemic mitral or other organic MV diseases [(4)].

Prognostics (risk factors) accused of residual mitral regurgitation (MR) after the setting of AVR are not clearly demonstrated in the literature and still questionable. Yet, they're different in either of severe AS or AR [(5)]. Moreover, fewer reports have assessed the clinical effect of moderate FMR in those patients subjected to AVR and further fewer have particularly traced the concomitant preoperative prognostics that would affect survival and might predict heart failure outcome [(4)].

This study primarily was aimed at investigating, analyzing and identifying the preoperative predictors (risk factors) that may predict residual MR and its adverse changes in patients with severe AV disease (AS or AR) and moderate FMR subjected to AVR with or without MV ring annuloplasty repair. This is in a trial to help wise decision-making for proper management of the moderate FMR (whether to repair surgically or treat



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it further medically) to avoid the postoperative adverse outcomes by providing a valid information key tool for the operator during the confusing preoperative decision-making time.

## PATIENTS AND METHODS

This retrospective comparative study included a total of 87 patients who presented with severe AS or AR (necessitating AVR) associated with moderate secondary (functional) MR, attending at Department of Cardiothoracic Surgery, Faculty of Medicine, Cairo University, Cairo, Cardiothoracic Surgery, Faculty of Medicine, Beni-Suef University, and in El Borg Hospital, Mohandiseen, Giza. This study was conducted between January 2019 to February 2023.

Patients were divided into two groups based on the type of surgical intervention done:

**Group (I)** that included 40 patients who were subjected to AVR only and **Group (II)** that included 47 patients who were subjected to AVR and MV ring annuloplasty repair.

All the data were studied and thoroughly evaluated in the preoperative, intraoperative, and over one-year postoperative periods and comparative analysis was done.

### Inclusion criteria:

Patients diagnosed with severe AS or AR associated with moderate secondary (functional) MR (MR due to mitral annular dilatation with preserved MV apparatus showing insignificant structural nor intrinsic valvular pathology echocardiographically evidenced). All candidates had normal coronaries.

### Exclusion criteria:

Patients with mild or severe FMR, patients with structural or intrinsic MV disease, patients with mitral stenosis (MS), patients undergoing other procedures involving coronary artery bypass grafting (CABG) or right heart valve procedures, patients with severe AR due to big ventricular septal defect (VSD), infective endocarditis or aortic dissection/aneurysm, patients with severe AS due to hypertrophic obstructive cardiomyopathy (HOCM), re-do and emergency-listed cases and extremes of age (less than 17 and more than 75 years).

## MANAGEMENT PROTOCOL

### (1) Preoperatively:

The assessed preoperative variables were age, gender, smoking, history of rheumatic fever, functional class according to the New Yok Heart Association (NYHA) classification, complete general and local cardiological clinical evaluation, hypertension, cerebrovascular accidents (CVAs), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), AF, body surface area (BSA)($m^2$), routine preoperative laboratory investigations (complete blood count (CBC), liver and renal function tests, coagulation profile, serum electrolytes (sodium and potassium), fasting blood glucose (FBG)), resting 12-lead electrocardiogram (ECG), plain chest X-ray and cardiac catheterization. Preoperative baseline Transthoracic Echocardiography (TTE) was done to provide the classic parameters: Left atrial diameter (LAD); Left ventricular end-diastolic diameter (LVEDD); Left ventricular end-systolic diameter (LVESD); Left ventricular Ejection Fraction per cent (LVEF%); Septal wall thickness (SWT); Posterior wall thickness (PWT); aortic root diameter; Right ventricular diameter (RVD); Fraction of shortening per cent (FS%); pulmonary artery pressure (PAP), peak and mean AV gradients, and the specific parameters: functional anatomy of the MV apparatus by assessing the mitral annulus, MV area, chordal and papillary muscles geometry (Abascal's "Wilkon's" echocardiographic score) and quantification of MR by measuring: regurgitant jet volumes, flow convergence surface area (zone) and anatomic regurgitant orifice area. The following variables were collected from the TTE: LVEDD, LVESD, LAD, LVEF%, MR jet area ($cm^2$), PAP, peak and mean AV gradient. Accordingly, MR was graded as Grade 1 (Mild MR) with jet area of 0.1-4.0 $cm^2$ and < 20% regurgitant fraction, Grade 2 (Moderate MR) with 4.0-8.0 $cm^2$ jet area and 20-40% regurgitant fraction, Grade 3 (Moderate-Severe MR) with 8.0-12.0 $cm^2$ jet area and 40-60% regurgitant fraction and Grade 4 (Severe MR) with jet area >12.0 $cm^2$ and >60% regurgitant fraction [6,7].

### (2) Intraoperatively:

The examined operative factors were intraoperative mortality, aortic cross clamping (ischemic) time, cardiopulmonary bypass (CPB) time, inotropic support demand, and the outcomes of the Transesophageal Echocardiography (TEE) performed during surgery.

### (3) Operative Technique:

All patients were given intravenous midazolam (0.1 mg/kg) prior to surgery, and they were all closely monitored throughout the procedure with an electrocardiogram, invasive arterial blood pressure using an arterial catheter connected to a pressure transducer, a central venous catheter inserted in the internal jugular vein, a nasopharyngeal temperature probe, pulse oximetry, capnography, a urinary catheter, and frequent arterial blood gases (ABGs) measurements for pH, electrolytes and glucose every 15 minutes. In order to maintain blood glucose levels between 110 and 150 mg/dl, diabetic patients underwent intraoperative tight (strict) glycemic management using a standard intravenous insulin infusion regimen (made by combining 100 units of insulin with 50 ml of 0.9% normal saline). Anaesthesia was induced throughout. Heparin (300–400 IU/kg) was administered in the beginning to start the anticoagulation process and subsequent doses were given as needed to keep the active clotting time (ACT) over 400 s throughout the

bypass period. Regardless of the overall amount of heparin used, protamine chloride reversed heparin at the conclusion of CPB at a 1:1 ratio of the loading dose. Patients were regularly cleaned and had their chests exposed by drapes.

After a standard median sternotomy, pericardiotomy, and suspension of the pericardial edges, the ascending aorta was cannulated.

Group (I) patients then underwent a two-stage common right atrial cannulation, while group (II) patients underwent bicaval cannulation, which involved placing separate venous cannulas in the superior (SVC) and inferior (IVC) vena cavae. A two-way cannula was placed in the aortic root for venting and the administration of first antegrade cardioplegia. Following aortotomy, cardioplegic fluid was then installed selectively directly into the coronary ostia. After the CPB was implemented, cooling occurred until the systemic temperature reached 28–30°C.

The aorta was then cross-clamped, and cold crystalloid cardioplegia was selectively intermittently infused antegradely for the first 45 minutes and thereafter every 30–40 minutes to preserve the myocardium. Using metallic bileaflet prosthesis (sized 21–23 mm St. Jude), all patients were submitted for AVR. Group II members had combined MV repair with a ring annuloplasty measuring 28 to 32 mm through a left atriotomy incision that used the Waterston groove as a guide. Any pathomorphological alterations were carefully evaluated by visualization of the MV apparatus in order to substantiate the preoperative TTE description. Following the surgery, the patient was rewarmed to 37°C, the aorta was declamped following de-airing maneuvers, and all electrolyte and acid-base imbalances were resolved. Afterward, the patient was weaned off of bypass.

**(4) Postoperatively:**

The assessed postoperative variables included hemodynamic status in the ICU, duration of mechanical ventilation, duration of inotropic support, total ICU stay, operative mortality (death during the early 30 days after surgery), morbidity, and adverse complications during hospital stay (Based on the number of patients who experienced at least one hospital problem, the total hospital complication rate was determined), total duration of hospital stay, routine prior-to-discharge TTE (for comparable standard and specific measurements), late mortality (death after the early 30 days post-surgery), postoperative one-year morbidity, complications, complete general and cardiological assessment with NYHA functional class, and one-year follow-up TTE (for comparable standard and specific measurements).

**Ethical Approval:**

**The study was conducted in the cardiothoracic surgery operating theaters of Cairo University, Beni-Suef University and El Borg Hospital. It was approved by the Research Ethics Committee (REC) with approval number of FMBSUREC/09042023/ Elbatanony. Each patient completed a written informed consent form to take part in the trial. The conduct of this study was guided by the Helsinki Declaration, the World Medical Association's rule of ethics for human studies.**

***Statistical analysis***

SPSS V21.0. For qualitative data, frequency and percent distributions were calculated using *Chi*-square test or *Fischer's exact* test when appropriate. For quantitative data, mean, standard deviation (SD), minimum and maximum were calculated and were compared using *t*-student test. Correlation between parameters was performed using *Spearman's rank correlation coefficient*. *Cox proportional hazards models* were used solely for AS and AR populations. Analysis of prognostics (risk factors) involved in mortality, residual MR and congestive heart failure adverse outcomes selectively in either AS or AR populations were performed by multivariable logistic regression analysis and *Bonferroni corrections* for multiple tests were applied as appropriate. In all tests, *p* value was considered significant when $p< 0.05$.

**RESULTS**

The whole study population was composed of 87 patients. Their ages ranged from 31-69 years with a median age of 49.5 years. 49(56.32%) were males and 38(43.68%) were females. AS patients represented 46(52.87%) and AR patients represented 41(47.13%).

All the patients had grade 2 moderate secondary FMR with no echocardiographic evidence of ruptured chordae tendineae, MV leaflets prolapse, marked MV annular or leaflets calcification or combined MS. Group (I) included 40(45.98%) patients who were subjected to AVR only. Group (II) included 47(54.02%) patients who were subjected to AVR and MV ring annuloplasty repair. History of rheumatic fever was positive in 20(50%) of group (I) and 25(53.20%) of group (II) ($p$=0.459). There were bilateral pulmonary fine basal crepitations in 2(5%) of group (I) and 3(6.38%) of group (II) ($p$=0.847).

The anti-failure medicine dosages used by the two groups did not differ in any statistically significant ways. Laboratory tests were normal, and neither group's changes were statistically different. Chest X-ray revealed cardiomegaly with increased cardio-thoracic ratio (C/T ratio) in both groups with a mean C/T ratio of 0.72±0.06 in group (I) and 0.74±0.05 in group (II) ($p$=0.465). The mean LVEDD, LVESD and LAD were 6.73±0.55, 4.68±0.98 and 4.55±0.58 versus 6.80±0.90, 4.72±0.77 and 4.49±0.67 in AS and AR populations respectively (Table 1).

**Table (1):** Preoperative characteristics and echocardiographic findings.

| | Group (I) | Group (II) | *p* value |
|---|---|---|---|
| **Age (years)** | 50.32 ± 4.21 | 53.56 ± 3.98 | 0.638 |
| **Males (%)** | 23(57.5%) | 26(55.32%) | 0.584 |
| **Females (%)** | 17(42.5%) | 21(44.68%) | 0.678 |
| **AS (%)** | 22(25.29%) | 24(27.59%) | 0.712 |
| **AR (%)** | 18(20.69%) | 23(26.44%) | 0.398 |
| **NYHA class III-IV (%)** | 33(82.5%) | 39(82.98%) | 0.437 |
| **Hypertension (%)** | 18(45%) | 21(44.68%) | 0.610 |
| **CVAs (%)** | 2(5%) | 3(6.38%) | 0.847 |
| **DM (%)** | 15(37.5%) | 18(38.30%) | 0.831 |
| **COPD (%)** | 1(2.5%) | 1(2.13%) | 0.991 |
| **AF (%)** | 18(45%) | 22(46.81%) | 0.747 |
| **Syncope (%)** | 6(15%) | 3(6.38%) | 0.562 |
| **BSA($m^2$)** | 1.76 ± 0.20 | 1.74 ± 0.41 | 0.079 |
| **LAD (cm)** | 4.47±0.54 | 4.51±0.80 | 0.071 |
| **LVEDD (cm)** | 6.79±0.85 | 6.85±0.92 | 0.069 |
| **LVESD (cm)** | 4.69±0.98 | 4.81±0.71 | 0.060 |
| **LVEF%** | 58.59±2.51 | 59.63±1.98 | 0.887 |
| **MR jet area ($cm^2$)** | 5.47±1.35 | 5.52±1.30 | 0.869 |
| **PAP (mmHg)** | 44.45±3.96 | 41.68±6.12 | 0.654 |
| **Peak AV gradient (mmHg)** | 78.21±19.40 | 79.55±19.54 | 0.781 |
| **Mean AV gradient (mmHg)** | 51.87±12.6 | 53.26±13.01 | 0.766 |

SD: standard deviation; NYHA: New Yok Heart Association classification; CVAs: cerebrovascular accidents; DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease; AF: atrial fibrillation; BSA: body surface area; LAD: left atrial diameter; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LVEF%: left ventricular ejection fraction per cent; MR: mitral regurgitation; PAP: pulmonary artery pressure; AV: aortic valve.

There was no intraoperative mortality. Intraoperative TEE was used before initiation of CPB and after weaning off it. In the post-CPB TEE, it showed downgrading of the degree of MR to grade 1 (mild MR) in 25(53.20%) of group (II) while it remained grade 2 (moderate MR) in group (I) (p=0.01). Metabolic acidosis was monitored in 10(25%) of group (I) and 8(17.02%) of group (II) (*p*=0.254). It was corrected efficiently before transferring to the ICU and no one faced persistent acidosis. Smooth weaning off bypass was achieved in the majority of both groups and the rest needed either inotropic support or electrical cardioversion to achieve weaning. All the patients were transferred to the ICU hemodynamically stable on epinephrine infusion 5 microgram/kg/min. Norepinephrine infusion 5-10 microgram/kg/min. was added to 11(27.5%) of group (I) and 13(27.66%) of group (II) (*p*=0.841) to control diabetic vasculopathy. Although group (II) showed statistically significant longer periods of total aortic cross clamping time, total CPB time and total operative time, there was no negative reflection on the intraoperative mortality or outcomes (Table 2).

**Table (2):** Operative results.

| | Group (I) | Group (II) | *p* value |
|---|---|---|---|
| **Mean total operative time (min.)** | 121.85± 20.56 | 149.74± 29.21 | **0.001** |
| **Mean total CPB time (min.)** | 79.11± 7.02 | 104.25± 3.69 | **0.001** |
| **Mean total cross clamping time (min.)** | 45.23± 6.54 | 75.10± 5.23 | **0.001** |
| **Smooth weaning off CPB (%)** | 33 (82.5%) | 39(82.98%) | 0.855 |

SD: standard deviation; CPB: cardiopulmonary bypass.

All the patients were transferred to the ICU mechanically ventilated. Then they were moved to the zone when hemodynamically stable after removing the draining thoracostomy tubes. We had 2(4.25%) operative mortalities in group (II): one from the AS populations due to intractable congestive heart failure and the other from the AR populations due to respiratory failure. No deep wound infection, pleural or pericardial effusions, gastrointestinal bleeding or acute renal failure were faced. Both groups showed comparable statistically insignificant postoperative outcomes. Although there were minute improvements of the TTE (done during hospital stay prior-to-discharge) parameters in both groups, only of statistically significance were the downgrading of the FMR degree and the decrease in MR jet area in group (II) (Table 3).

**Table (3):** Postoperative outcomes and echocardiographic findings.

| | Group (I) | Group (II) | *p* value |
|---|---|---|---|
| **Mean duration of mechanical ventilation (hours)** | 6.14±2.25 | 7.21±2.63 | 0.421 |
| **Mean duration of inotropic support (hours)** | 15.91±3.81 | 17.46±3.20 | 0.258 |
| **Mean total blood loss (ml)** | 440±108.1 | 435±106.1 | 0.646 |
| **Mean total duration of ICU stay (hours)** | 42.98±7.23 | 45.55±6.23 | 0.232 |
| **Congestive heart failure (%)** | 2(5%) | 1(2.12%) | 0.467 |
| **AF (%)** | 18(45%) | 22(46.81%) | 0.747 |
| **Transient heart block (%)** | 0(0%) | 2(4.25%) | 0.091 |
| **CVA (%)** | 0(0%) | 1(2.12%) | 0.101 |
| **Re-exploration for bleeding (%)** | 2(5%) | 2(4.25%) | 0.687 |
| **Superficial wound infection (%)** | 10(25%) | 11(23.40%) | 0.569 |
| **Respiratory complications (%)** | 0(0%) | 1(2.5%) | 0.181 |
| **Mean total duration of hospital stay (days)** | 8.59±1.98 | 9.42±2.24 | 0.236 |
| **The overall hospital complication rate (%)** | 9(22.5%) | 12(25.53%) | 0.098 |
| **Operative mortality (%)** | 0(0%) | 2(4.25%) | 0.092 |
| **Operative mortality among AS/AR populations (%)** | 0(0%)/ 0(0%) | 1(4.16%)/ 1(4.34%) | 0.093 |
| **LAD (cm)** | 4.46±0.78 | 4.45±0.23 | 0.070 |
| **LVEDD (cm)** | 6.74±0.12 | 6.80±0.56 | 0.055 |
| **LVESD (cm)** | 4.64±0.77 | 4.76±0.12 | 0.059 |
| **LVEF%** | 54.73±0.86 | 54.07±0.56 | 0.848 |
| **MR jet area ($cm^2$)** | 5.30±0.87 | 4.01±0.51 | **0.001** |
| **PAP (mmHg)** | 41.73±1.62 | 38.52±3.58 | 0.545 |
| **Grade 1 MR** | 0(0%) | 25(53.20%) | **0.001** |
| **Grade 2 MR** | 40(100%) | 20(42.55%) | **0.001** |

SD: standard deviation; ICU: intensive care unit; AF: atrial fibrillation; CVA: cerebrovascular accidents; LAD: left atrial diameter; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LVEF%: left ventricular ejection fraction per cent; MR: mitral regurgitation; PAP: pulmonary artery pressure.

After discharge from the hospital, the study populations were called after a mean period of 340.61±25.84 days. The cumulative duration of the study was 4.08 years. We had 2(5%) late mortalities in group (I) from the AS populations due to intractable congestive heart failure. No other major cardiac morbidities or CVAs were recorded. There was statistically significant improvement in NYHA class, FMR degree and MR jet area in group (II) (Table 4).

**Table (4):** One-year follow-up results and echocardiographic findings.

| | Group (I) | Group (II) | *p* value |
|---|---|---|---|
| **Late mortality (%)** | 2(5%) | 0(0%) | 0.097 |
| **Late mortality among AS/AR populations (%)** | 2(9.09%)/ 0(0%) | 0(0%)/ 0(0%) | 0.071 |
| **The overall survival rate (%)** | 38(95%) | 45 (95.74%) | 0.845 |
| **NYHA class I (%)** | 22(57.89%) | 38 (84.44%) | **0.001** |
| **NYHA class II (%)** | 16(42.10%) | 7(15.55%) | **0.001** |
| **LAD (cm)** | 4.45±0.23 | 4.36±0.56 | 0.057 |
| **LVEDD (cm)** | 6.62±0.01 | 6.65±0.11 | 0.054 |
| **LVESD (cm)** | 4.52±0.21 | 4.61±0.43 | 0.058 |
| **LVEF%** | 60.12±1.09 | 60.82±1.50 | 0.869 |
| **MR jet area ($cm^2$)** | 4.05±0.67 | 3.30±0.81 | **0.001** |
| **PAP (mmHg)** | 30.22±0.17 | 29.18±0.23 | 0.601 |
| **Grade 1 MR** | 18(47.36%) | 35(77.77%) | **0.001** |
| **Grade 2 MR** | 20(52.63%) | 10(22.22%) | **0.001** |

SD: standard deviation; NYHA: New Yok Heart Association classification; LAD: left atrial diameter; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LVEF%: left ventricular ejection fraction per cent; MR: mitral regurgitation; PAP: pulmonary artery pressure.

Both groups showed statistically significant results at one-year follow-up compared to the preoperative baseline criteria and group (II) showed much better statistically significant results compared to group (I) as regards the MR jet area and grade of FMR that was reflected positively on the statistically significant improvement in NYHA class and marked improvement of LAD. Cardiac dimensions (LVEDD and LVESD) showed more improvement very close to significance ($p$= 0.054 and $p$= 0.058; respectively) in group (II) denoting better reverse cardiac remodeling as

compared to group (I). Both groups showed improvement of the LVEF% but this wasn't statistically significant (Table 5).

**Table (5):** One-year follow-up echocardiographic changes versus preoperatively.

| | Group (I) | | | Group (II) | | |
|---|---|---|---|---|---|---|
| | **MD** | ***p* Value** | **95% CI** | **MD** | ***p* Value** | **95% CI** |
| **LAD (cm)** | 0.240 | 0.032 | 0.029–0.380 | 0.360 | 0.001 | 0.042–0.538 |
| **LVEDD (cm)** | 0.948 | 0.001 | 0.756–1.128 | 1.010 | 0.001 | 0.813–1.290 |
| **LVESD (cm)** | 0.510 | 0.001 | 0.183–1.042 | 0.450 | 0.001 | 0.279–1.014 |
| **LVEF%** | 1.812 | 0.614 | 0.921–8.031 | 2.010 | 0.604 | 1.331–7.412 |
| **MR Jet area ($cm^2$)** | 1.650 | 0.01 | 0.857-4.989 | 2.601 | 0.001 | 1.154-4.356 |

MD: mean difference; CI: confidence interval; LAD: left atrial diameter; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LVEF%: left ventricular ejection fraction per cent; MR: mitral regurgitation.

The presence of preoperative FMR grade 2 wasn't associated with independent adverse effects on one-year overall survival rate in patients with either AS [HR= 1.5 (95% CI= 0.610-3.145); *p*= 0.1] or AR [HR= 1.3 (95% CI= 0.465-3.798); *p*= 0.3]. One-year overall survival rate was 43(93.48%) and 40(97.56%) in AS and AR populations respectively (*p*=0.646). In both groups of the study, the overall mortality was 4(4.59%), the intraoperative mortality was 0%, the operative mortality was 2(2.29%) and the late mortality was 2(2.29%). Among AS populations, the overall mortality was 3(6.52%): 1(4.16%) operative mortality in group (II) and 2(9.09%) late mortality in group (I). Among AR populations, the overall mortality was 1(2.43%) resembling 1(4.34%) operative mortality in group (II). Among old age, AF, decreased preoperative LVEF% and residual MR as being identified risk factors that had adverse effects on mortality, only AF and residual MR were found to be statistically significant predictors of overall mortality after surgery by multivariable analysis (Table 6).

**Table (6):** Risk factors of postoperative overall mortality by multivariable logistic regression analysis.

| Risk Factor | HR | *p* Value | 95% CI |
|---|---|---|---|
| AF | 2.57 | 0.011 | 1.188-6.067 |
| Residual MR | 3.42 | 0.001 | 1.024–11.756 |

AF: Atrial fibrillation; MR: mitral regurgitation; HR: hazard ratio; CI: confidence interval

Postoperative residual persistent MR proved to be the most hazardous predictor for postoperative morbidity and mortality. Postoperatively prior to hospital discharge, residual MR was recorded in 32(71.11%) of AS populations: 22(100%) and 10(43.47%) of groups (I) and (II) respectively (*p*= 0.001). For AR populations, residual MR was recorded in 28(70%): 18(100%) and 10(45.45%) of groups (I) and (II) respectively (*p*= 0.001). By multivariable analysis, the unattempting of MV repair and prolonged inotropic support in the ICU were the statistically significant predictors of early (within 30 days postoperatively) residual MR, and AF, higher postoperative FMR grades and larger LAD were the statistically significant predictors of late (after 30 days postoperatively) residual MR (Table 7).

**Table (7):** Predictors of postoperative residual MR by multivariable logistic regression analysis

| Risk Factor | OR | *p* Value | 95% CI |
|---|---|---|---|
| **Early residual MR** | | | |
| No MV repair | 3.12 | 0.007 | 1.365–21.504 |
| Prolonged inotropic support | 1.03 | 0.015 | 0.50–3.012 |
| **Late residual MR** | | | |
| AF | 3.15 | 0.046 | 1.851–6.343 |
| Postoperative FMR grade 2 or more | 1.8 | 0.008 | 1.072–2.998 |
| LAD >5 cm | 2.11 | 0.054 | 0.225–4.562 |

AF: Atrial fibrillation; MR: mitral regurgitation; LAD: left atrial diameter; OR: odds ratio; CI: confidence interval.

The strong association of residual MR and the development of congestive heart failure outcome with subsequent multiple adverse events and mortality makes it the most important variable to be evaluated. At one-year follow-up, residual MR was recorded in 17(39.53%) of AS populations: 12(60%) and 5(21.74%) of groups (I) and (II) respectively (*p*= 0.001). For AR populations, residual MR was recorded in 13(32.50%): 8(44.44%) and 5(22.72%) of groups (I) and (II) respectively (*p*= 0.001). Significant prognostics (risk factors) associated with the development of persistent residual MR were found to be different in either of AS or AR patients. They included AF, LAD >5 cm, preoperative peak AV gradient <60 mmHg and preoperative mean AV gradient <40 mmHg in AS populations. Patients with AR associated with preoperative LVESD <4.5 cm makes them at higher risk of the residual MR (Table 8).

**Table (8):** Prognostics of postoperative residual MR in AS and AR populations by multivariable logistic regression analysis

| Risk Factor | OR | *p* Value | 95% CI |
|---|---|---|---|
| **AS** | | | |
| AF | 3.9 | 0.01 | 1.101- 10.125 |
| LAD >5 cm | 3.5 | 0.002 | 1.236- 8.612 |
| Preoperative peak AV gradient <60 mmHg | 1.9 | 0.01 | 1.140- 4.023 |
| Preoperative mean AV gradient <40 mmHg | 1.7 | 0.02 | 1.090, 3.554 |
| **AR** | | | |
| Preoperative LVESD <4.5 cm | 5.2 | 0.001 | 1.850–15.986 |

AS: aortic stenosis; AF: Atrial fibrillation; LAD: left atrial diameter; AV: aortic valve; AR: aortic regurgitation; LVESD: left ventricular end-systolic diameter; OR: odds ratio; CI: confidence interval.

## DISCUSSION

Variable degrees of FMR are encountered in diagnosed cases with severe AV disease and it contributes to AF, frequent congestive heart failure episodes, pulmonary hypertension and possibly CVAs including stroke [8,9]. It's settled that severe FMR has to be intervened during AVR operation. However, lesser degrees didn't have clear cut decisions with class IIb recommendation [10,11,12]. It's assumed that reversed LV remodeling after AVR would reverse the MV annular changes and consequently it would improve FMR [13-15].

Although some reports demonstrated postoperative improvement of the moderate FMR in some survivors without surgical intervention [1,13,14,16,17], others deny the capability of the reverse remodeling AVR to make significant improvement in the degree of FMR and they stress on the need for surgical correction [3,5,6,8,9,18-24].

In comparison to other studies, our comparative cohort showed younger age, relatively similar gender distribution, more homogeneity with semi-equality of representation of both AV pathologies in either group and comparable preoperative baseline co-morbidities and TTE parameters although some studies reported on a larger sample sized yet heterogenous cohorts. However, prior studies gave no data or correlation between the MR jet area and its changes and influences on the moderate FMR and the development of residual MR; a parameter stressed upon in our study. None gave any reports on the usage or doses of the preoperative anti-failure medical treatment which should influence the functional medical status of the preoperative profile of the study populations. Recorded values of LVEDD, LVESD, LAD, peak and mean AV gradients in our cohort were like other reports [3,4,5,9,13,24,25]. Reported studies were mostly retrospective.

Intraoperatively, group (II) showed statistically significant longer durations of total aortic cross clamping time, total CPB time and total operative time. However, there weren't any negative impacts on the intraoperative mortality or the operative outcomes. These findings illustrate that moderate FMR repair didn't add negative risks to the combined surgery. These results were similarly reported by other authors [3,4,5,9,13,24,25,26]. The post-CPB TEE's informational data and its analysis about the efficacy of MV repair and degree of residual MR were seldomly reported in previous studies. These significant results add more proof to the positive impact of adding MV repair in the combined procedure. We faced no intraoperative mortality in either group; the same as what was reported by **Shingu *et al.* [5]. Coutinho *et al.* [13]** reported 0.3% mortality.

In the early postoperative period, both groups showed statistically insignificant differences. The operative mortality was 2(4.25%) in group (II) compared to none in group (I) ($p$=0.092). Again, the operative mortality among AS and AR populations in either group was also statistically insignificant ($p$=0.093). Our findings give an additional proof that repair of the moderate FMR didn't add burden or more risk in the early postoperative period and it even provided better echocardiographic parameters. **Wan *et al.* [4]** reported 72% improvement of the MR grade to grade 1 MR, 26% remained grade 2 MR and 2% worsened to grade 3 MR. Operative mortality rate was 5% by **Wan *et al.* [4]**, 3.6% by **Sorabella *et al.* [24]**, 2.6% by **Koji *et al.* [25],** 1.1% by **Coutinho *et al.* [13]** and 0% by **Shingu *et al.* [5]**.

The overall survival rates of group (I) and group (II) were 38(95%) and 45(95.74%) representing statistically insignificant difference ($p$=0.845). No patient of either group had worsened MR grade or needed re-operation for MR. Our findings gave a proof that LV reverse remodeling and LAD diminution occurred more in the combined surgery group, and it would progress on longer-term follow-up periods giving more evident significant results. We can also conclude that better LV reverse remodeling is associated with better improvement in the postoperative MR grade. This conclusion was previously documented by **Unger *et al.* [8]** who reported that the better the magnitude of the LV reverse remodeling, the more the reduction of the MR grade. Over 4.08 years which was the cumulative duration of our study, we could conclude that MV repair has a positive effect on survival, the functional clinical status, cardiac reverse remodeling and the degree of FMR preventing its worsening. Moreover, intraoperative downgraded MR degree may predict its postoperative improvement. Other authors reported similar findings. **Wan *et al.* [4] and Shingu *et al.* [5]** in their 3.8±3.6 years and 28 months studies respectively reported the same results with 66.67% improvement of FMR and 33% remained with residual grade 2 MR.

At one-year follow-up, the overall mortality rate for the whole cohort was 4(4.59%). The overall survival rate was 43(93.48%) and 40(97.56%) in AS and AR populations respectively representing statistically insignificant difference ($p$=0.646). We can conclude that the combined MV repair surgery didn't affect the overall survival rate in either AS or AR patients. Other authors reported similar conclusion [4,20]. **Coutinho *et al.*** [13] reported similar results with 1,5 and 10-years overall survival rates 93±2.8%, 84.2±4.2% and 76.7±5.7% respectively. **Shingu *et al.*** [5] reported 5-years 100% survival rate.

Although the preoperative grade 2 FMR per se wasn't found to be associated with poor overall survival rate at one-year postoperatively for either AS or AR patients, the presence of associated preoperative risk factors had been found to be responsible for the adverse effects and mortality. This finding was reported by other researchers [3,4,5,9,13,24,25]. It was found that the postoperative residual MR was strongly associated with higher overall mortality rate (including operative and late mortalities). This can be explained by the tight association between residual MR and congestive heart failure outcomes that might be intractably lethal (as what was faced with our lost 3 old AS patients). **Ruel *et al.*** [3] reported that patients with residual MR carried a higher level of risks of congestive heart failure adverse outcomes up to death when preoperative grade 2 FMR was associated with one or more risk factor like AF and higher preoperative AV gradients. Only one study conducted by **Barreiro *et al.*** [6] identified preoperative grade 2 FMR as a risk factor for early mortality but other authors argued and disputed that conclusion [3,4,20,21].

While **Barreiro *et al.*** [6] reported that the preoperative grade 2 FMR was an independent predictor of late mortality in their study that involved mixed organic and functional MR, **Ruel *et al.*** [3] reported that the preoperative grade 2 FMR per se wasn't associated with any independent adverse effects or late mortality in AS or AR patients. In a recent review, even 10-years mortality wasn't affected by the preoperative grade 2 FMR [13]. Multivariable logistic regression analysis showed that among old age, AF and decreased preoperative LVEF%, persistent AF was another statistically significant predictor of overall mortality. **Coutinho *et al.*** [13] reported that persistent MR was the most powerful predictor for early and late mortality and severely compromised long-term survival. They stressed on that the most important risk factor for survival was the early residual MR and subsequently they recommended MV repair.

In our study, early and persistent late residual MR was found to be the most adverse factor involved in hazardous morbidity and mortality. It was evident that significantly higher rates of residual MR developed in the non-MV repair populations of either AS or AR patients during both the early and late postoperative periods giving added pro for the combined MV repair surgery. The predictors of residual MR are still debatable and the listed ones in the literature are AF, LAD >5 cm and PAP >50 mmHg [1,5].

Multivariable logistic regression analysis showed that unattempting of MV repair and prolonged inotropic support in the ICU were the statistically significant predictors of early residual MR while postoperative FMR grade 2 or more, persistent AF and LAD >5 cm were the statistically significant predictors of persistent late residual MR. PAP wasn't found to be a risk factor in our study most probably because it wasn't preoperatively high and it improved postoperatively in both study groups with statistically insignificant difference. **Coutinho *et al.*** [13] reported similar results. They reported absence of MV surgery, aortic root enlargement, prolonged postoperative inotropic support and (AF: close to significance) were the statistically significant predictors of early residual MR while postoperative FMR grade 2 or more, persistent AF (at hospital discharge) and (larger LAD: close to significance) among others including acute renal failure were the statistically significant predictors of late residual MR. **Shingu *et al.*** [5] reported that AF and LAD >5 cm were the statistically significant predictors of residual MR. **Matsumura *et al.*** [27] reported long-term AF and non-MV surgery were independent predictors of residual MR. **Wan *et al.*** [4] reported higher preoperative tricuspid regurgitation and un-improvement of intraoperative FMR with anesthesia were independent predictors of early residual MR while presence of cerebrovascular disease and higher preoperative LVEF% were independent predictors of late residual MR.

The main target of our study is to identify the preoperative risk factors that would be responsible for suboptimal outcomes, and this resembles the principal and the most important finding of this study. Preoperative predictive risk factors involved in the development of residual MR among AS populations were found to be AF, LAD >5 cm, peak AV gradient <60 mmHg and mean AV gradient <40 mmHg while LVESD <4.5 cm was found to be the most important risk factor for AR patients. We thus concluded that in AS patients, the postoperative surplus or even progression of the preoperative FMR grade 2 depends on the presence of one or more risk factor and in AR patients, normal or small sized LV is riskier than a dilated one that is well-known for better respond to reverse cardiac remodeling. The sequence of congestive heart failure secondary to residual MR is markedly associated with the concomitant preoperative risk factors in AS patients that reflect the poorly affected cardiac condition, the longer duration of FMR and the more advanced LV diastolic dysfunction; and thus, they resemble the risk factors for the congestive heart failure postoperatively. Thus, patients with AS without associated preoperative risk factors may survive well even with residual MR because of non-severely affected heart and so MV repair would be unnecessary. The

presence of the associated risks strongly reflects the longstanding physiologically substantial FMR that seems to be unlikely to improve alone without any surgical intervention to the MV. Thus, moderate FMR per se could be considered a significant indicator of a more severely affected heart disease rather than an etiological agent. Large LAD may strongly refer to dilated MV annulus (Carpentier type I) [8], that may predispose to residual MR without MV repair or with a failed attempt of repair. Postoperative peak and mean AV pressure changes may be more limited in patients with diminished preoperative gradients than those with higher ones according to factor 1 in the Lancellotti's review predisposing to residual MR due to persistent more LV to LA pressure gradient [8].

LV remodeling in AR patients is responsible for FMR and postoperative reverse remodeling helps in its correction. Reverse remodeling is more apparent with a dilated LV because it has a high postoperative size reduction potential. Thus, AR patients with a preoperative small or normal sized LV having a lower postoperative size reduction potential are at a higher risk of development of residual MR and congestive heart failure and so MV repair may be a necessity. These conclusions are agreed upon by other authors [3,4,5,8,9,13,24,25,28,29]. **Sabbah *et al.*** [2] agreed with our conclusion reporting that absence of associated preoperative risk factors makes fine postoperative outcomes like in patients with only FMR grade 1. Also, **Ruel *et al.*** [3] agreed with our conclusion. They reported that the incidence of residual MR increases with increasing the number of the associated risk factors in AS patients. They reported residual MR at 18 months postoperatively in 31.6% without risk factors, 36.5% with 1 risk factor and 55.6% with 2 risk factors. They also reported that the incidence of residual MR at 18 months postoperatively was 42.1% in AR patients with LVESD <4.5 cm and 20% in those with LVESD >4.5 cm.

**Shingu *et al.*** [5] reported that LAD >50 mm and mean AV gradient <40 mmHg were the significant predictors of residual MR in AS patients and their preoperative ratio >0.9 (mm/mmHg) was highly predictive of residual MR with a specificity of 74% and sensitivity of 70%. **Mangina *et al.*** [30] in their study that involved mixed organic and functional MR reported high relation between the preoperative LAD and PAP to the postoperative residual MR severity. However, they didn't correlate other TTE parameters to the functional clinical status of the survivors. **Bishay *et al.*** [31] illustrated the importance of the LAD as an index of the cardiac condition severity being a sensitive indicator for LV diastolic dysfunction as it is exposed to the LV filling pressures through the open mitral valve orifice during diastole and its size should therefore be influenced by the same factors that determine the diastolic filling pressure on the LV. **Barreiro *et al.*** [6] in their long-term study concluded lower survival rates for patients with preoperative FMR grade 2. However, their study involved mixed organic and functional MR (48% of their cohort), only examined long-term life quality, didn't refer to any associated preoperative risk factors that interfered in the postoperative outcome and TTE was done for only 50% of their cohort. **Coutinho *et al.*** [13] reported that persistent long-term AF was not only an independent risk factor for residual MR but also it was associated with poor survival. **Mavromatis *et al.*** [32] in their study about risk factors of residual MR after transcatheter AV replacement (TAVR) reported lower BSA, AF/flutter, diminished mean AV gradient and increased LV dimension as risk factors.

## CONCLUSION

At one-year postoperatively, the preoperative grade 2 FMR per se is not associated with poor overall survival rate and is not an independent risk factor for postoperative mortality for either AS or AR patients. The postoperative residual MR with its congestive heart failure lethal sequelae is strongly associated with higher overall mortality rate (including operative and late mortalities). The presence of associated preoperative risk factors is responsible for the development of residual MR that is accused of the postoperative adverse effects and mortality. Preoperative predictive risk factors involved in the development of residual MR among AS populations are AF, LAD >5 cm, peak AV gradient <60 mmHg and mean AV gradient <40 mmHg while LVESD <4.5 cm is the most important risk factor for AR patients. In AS patients, the postoperative surplus or even progression of the preoperative FMR grade 2 depends on the presence of one or more risk factor. In AR patients, normal or small sized LV is riskier than a dilated one. We strongly recommend combined MV ring annuloplasty at the same setting of AVR for the moderate FMR when there are any of the forementioned preoperative risk factors.

### Study Limitations:

This study is retrospective research with a modestly sized case sample. The surgical recovery period is not very long. In order to verify the findings, longer follow-up times are required. Our demographic research groups were made up of younger age groupings than previous series. They might not have reflected the extremes of the patients' traits as a result. Results are limited to moderate FMR (grade 2 FMR) only as an etiology of the concomitant MR. Other aetiological entities weren't involved in this study. However, we provided clearly what can be considered a valid information key tool for the operator during the confusing preoperative decision-making time.

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