

# Mitral Valve Surgery for Functional Regurgitation: Insights into Heart Failure and Readmission

Joseph A. Gancayco<sup>1</sup>, Alexander P. Kossar<sup>1</sup>, Codruta Chiuзан<sup>2</sup>, Isaac George<sup>1\*</sup>

<sup>1</sup>Division of Cardiothoracic Surgery, New York Presbyterian Hospital, College of Physicians and Surgeons of Columbia University, New York, USA

<sup>2</sup>Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, USA  
Email: \*ig2006@cumc.columbia.edu

**How to cite this paper:** Gancayco, J.A., Kossar, A.P., Chiuзан, C. and George, I. (2022) Mitral Valve Surgery for Functional Regurgitation: Insights into Heart Failure and Readmission. *World Journal of Cardiovascular Surgery*, 12, 135-152.  
<https://doi.org/10.4236/wjcs.2022.126011>

**Received:** May 24, 2022

**Accepted:** June 27, 2022

**Published:** June 30, 2022

Copyright © 2022 by author(s) and Scientific Research Publishing Inc.

This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

## Abstract

**Background:** Functional mitral regurgitation (FMR) is a significant burden among our increasingly elderly population. Mitral valve repair (MVR) is the preferred surgical treatment of FMR despite limited evidence supporting its efficacy. Mitral valve replacement (MVR) is the alternative procedure typically reserved for patients who are at higher risk or refractory to MVR. The present study aims to determine which of the two procedures is more effective in the surgical treatment of FMR. **Methods:** 344 charts of FMR patients who received either MVR (n = 263) or MVR (n = 81) from 2004-2016 at our institution were reviewed. Treatment efficacy was assessed based on heart failure (HF)-readmission and survival rates within 5 years from discharge. Propensity score approach with inverse probability weighting and Cox regression models were employed to evaluate procedural impact on survival and rehospitalizations, respectively. Follow-up echocardiographic data from the original cohort was assessed for differences in metrics between procedural groups at >6 months (MVR: n = 75; MVR: n = 23) and 1 year (MVR: n = 75; MVR: n = 18) post-op. **Results:** MVR patients had a lower risk of being readmitted for HF within 5 years compared to the MVR group (HR-adj (95% CI): 0.60 (0.41 - 0.88), p = 0.008). MVR patients also had a higher overall risk of death (HR-adj (95% CI): 1.82 (1.05 - 3.16), p = 0.034) but this was borderline significantly different at 5 years cut-off (p = 0.057). **Conclusions:** Higher HF readmission in MVR patients than in sicker, higher surgical-risk MVR patients reflects the inadequacy of MVR to treat FMR. Novel approaches to MVR may be necessary to adequately manage FMR.

## Keywords

Mitral Regurgitation, Mitral Valve Repair, Mitral Valve Replacement, Heart

## 1. Introduction

Heart failure (HF) is currently the leading cause of hospital admission in patients over 65 and hospitalization accounts for 60% of total HF costs [1]. Functional mitral regurgitation (FMR) is characterized by a mitral valve (MV) with normal leaflet morphology, but whose coaptation is compromised due to geometric changes in other regions of the heart, namely the left ventricle. Strong relationships between FMR/mortality and FMR/HF-hospitalizations have been established. Grigioni *et al.* found that FMR was a significant predictor of long-term mortality [2], while others have found moderate to severe MR to be a strong independent predictor of both HF-hospitalization in patients with left ventricular ejection fraction (LVEF) <40% and 5-year mortality [3]. These results have been replicated by other studies, highlighting the need for a better understanding of the disease process and more effective surgical therapies [4] [5]. Presently, 2017 AHA/ACC consensus-guidelines state that if surgery is indicated for FMR, then mitral valve repair (MVR) should be favored with limited evidence support [6]. MV annuloplasty is the preferred repair option to treat FMR since a constriction of the annulus would intuitively restore leaflet coaptation. Bolling *et al.* were among the first to show that the use of undersized annuloplasties produced beneficial results *i.e.*, increased 24-month survival, however, recent studies have questioned the efficacy of this procedure [7] [8] [9]. Additionally, studies have found both classical repairs and replacements to be inadequate in treating FMR without complications and thus patients are typically treated with conservative medical therapy [10].

The purpose of this study was to evaluate the mid-term effectiveness of MV surgery for the treatment of FMR in detail by quantifying and comparing the HF readmission and overall mortality rates, understanding that bioprosthetic structural valve degeneration in the mitral position can occur as early as 5 years [11]. However, within a 5-year period, we hypothesize that MVR confers greater postoperative reduction of FMR, and therefore lowers MR recurrence and HF readmission rates, due to a more robust ventricular stabilizing effect than MVR.

## 2. Methods

### 2.1. Patient Selection

Retrospective data was obtained from the NewYork-Presbyterian Hospital Database. All patients undergoing MV surgery for FMR and primarily followed at our institution from 2004 to 2016 were included in this analysis (MVR: n = 263; MVR: n = 81); patients undergoing surgery but were followed by a cardiologist at an outside hospital were excluded from this analysis. Primary endpoints of interest included follow-up echocardiogram data, readmission at Columbia

University Irving Medical Center (CUIMC) or other New York-Presbyterian campuses, and mortality. Admission information from hospitals other than Columbia were obtained (n = 79) and included in this analysis. Functional MV disease was classified from an analysis of clinical records, operative reports, and echocardiograms. MV leaflets were identified to be normal but regurgitation across the valve indicating operation was present in all patients, and findings as outlined by the 2014 AHA-guidelines based on valve anatomy, valve hemodynamics, and associated cardiac findings were taken into account when classifying FMR based on noninvasive studies [12]. Patients with preoperative findings consistent with primary MR, active endocarditis, cardiogenic shock, and concomitant mechanical-assist-device implantation were excluded from the study (Figure 1) [4].

Patients undergoing MVr or MVR with any technique along with the presence or absence of other concomitant cardiac, aortic, or pacemaker procedures were included. MVr and MVR techniques are similar to previously described [13]. All rings were semi-rigid rings, and complete versus partial ring usage was at surgeon discretion. All replacement procedures underwent chordal sparing replacement when possible. Surgical risk was calculated for each patient using the STS-Risk-Calculator v2.81. Patients undergoing concomitant procedures that were not supported by the STS-calculator v2.81 were down-coded to either the isolated MV procedure or MV + coronary artery bypass graft (CABG) for inclusion for this analysis; this represents 61.98% of MVr and 53.75% of MVR (Table 1).

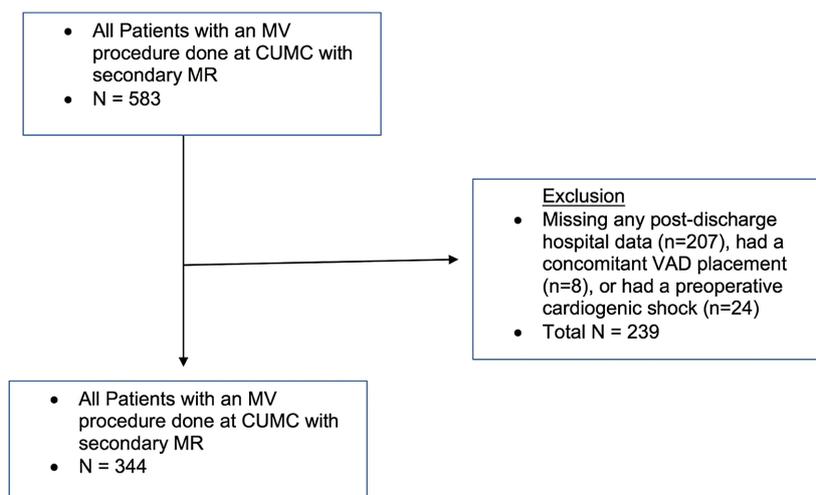


Figure 1. Selection criteria.

Table 1. Baseline characteristics—MVr vs MVR.

	MVr N = 263	MVR N = 81	P-value	Standardized Differences <sup>†</sup>
Age, median (IQR)	70 (62 - 78)	72 (63 - 80)	0.281	0.14
Age > 70	133 (50.57)	45 (55.56)	0.432	0.10
Gender(male)	157 (59.70)	44 (54.32)	0.390	0.11

**Continued**

LVEF, median (IQR)	37 (28 - 50)	45 (35 - 55)	0.004*	0.38
LVEDD, median (IQR)	5.7 (5.1 - 6.2)	5.5 (5 - 6)	0.173	0.23
NYHA-Class > 3	151 (57.41)	52 (64.20)	0.278	0.14
MR > 3	141 (53.61)	55 (67.90)	0.023*	0.30
TR > 3	15 (5.70)	14 (17.28)	0.001*	0.37
AI > 3	27 (10.27)	3 (3.70)	0.047*	0.26
Medical/Surgical History, n (%)				
CAD	184 (69.96)	57 (70.37)	0.944	0.01
MI	105 (39.92)	31 (38.27)	0.790	0.03
DM	93 (35.36)	21 (25.93)	0.115	0.21
CKD	22 (8.37)	14 (17.28)	0.022*	0.27
ESRD	10 (3.80)	4 (4.94)	0.747	0.06
COPD	29 (11.03)	7 (8.64)	0.539	0.08
HTN	193 (73.38)	57 (70.37)	0.595	0.07
AFib	99 (37.64)	27 (33.33)	0.482	0.09
Stroke	15 (5.70)	3 (3.70)	0.581	0.09
PAD	31 (11.79)	9 (11.11)	0.868	0.02
Cirrhosis	7 (2.66)	3 (3.70)	0.705	0.06
Previous Cardiac Surgery	59 (22.43)	22 (27.16)	0.381	0.11
Concomitant-Procedure, n (%)				
CABG	132 (50.19)	45 (55.56)	0.398	0.11
AVR	78 (29.66)	17 (20.99)	0.127	0.20
TVR	26 (9.89)	14 (17.28)	0.069	0.22
Other	38 (14.45)	19 (23.46)	0.057	0.23
STS-Scores, median (IQR)				
Risk-of-mortality	3.50 (1.85 - 5.74)	6.29 (3.22 - 11.11)	<0.0001*	0.62
Morbidity-or-mortality	25.36 (18.17 - 34.28)	34.69 (25.67 - 51.42)	<0.0001*	0.66
Long-length-of-stay	12.31 (7.27 - 17.63)	17.38 (12.44 - 27.73)	<0.0001*	0.66
Short-length-of-stay	18.09 (11.30 - 29.58)	11.43 (5.63 - 18.31)	<0.0001*	0.65
Permanent-stroke	2.26 (1.67 - 2.91)	2.54 (1.69 - 3.70)	0.086	0.23
Prolonged-ventilation	16.81 (10.70 - 25.46)	25.91 (16.96 - 36.81)	<0.0001*	0.62
DSW-infection	0.37 (0.23 - 0.58)	0.38 (0.24 - 0.54)	0.956	0.01
Reoperation	9.62 (7.59 - 12.15)	13.36 (10.52 - 16.84)	<0.0001*	0.82

Data are presented as frequencies and percentages (%) or median (interquartile range: IQR). \*Significant differences between MVR and MVR groups. †Standardized difference = difference in mean or proportions divided by the standard error; imbalance between groups was defined as absolute value greater than 0.10 (corresponding to a small effect size). LVEF indicates left ventricular ejection fraction; LVEDD, left ventricular end diastolic diameter; NYHA, New York Heart Association; MR, mitral regurgitation; TR, tricuspid regurgitation; AI, aortic insufficiency; CAD, coronary artery disease; DM, diabetes mellitus; MI, myocardial infarction; CKD, chronic kidney disease; ESRD, end stage renal disease; COPD, chronic obstructive pulmonary disease; HTN, hypertension; AFib, atrial fibrillation; PAD, peripheral artery disease; CABG, coronary artery bypass graft; AVR, aortic valve repair/replacement; TVR, tricuspid valve repair/replacement; Other, cardiac procedure (non mitral, aortic valve, tricuspid valve, or CABG); STS, Society of Thoracic Surgeons; DSW, deep sternal wound; IQR, interquartile range.

Thus, STS-statistics reported in this study are likely underestimations of actual surgical risk.

The study protocol was approved by the institutional review committee of CUMC and informed consent was waived.

## 2.2. Readmission Data

Readmission data was obtained from all New York-Presbyterian campuses any time after the initial surgery. Initial postoperative readmission was classified based on the first readmission after the index procedure. All subsequent readmissions within a 5-year period were included in the analysis. Time to readmission, and total number of readmissions were quantified.

Readmissions were causally classified as HF or non-HF based on chart review and adjudication by authors (J.A.G., I.G.) Readmission that involved MV-reoperation was classified as HF-related. Time to readmission was defined as the period between index discharges to the first day of readmission.

Patients who underwent orthotopic heart transplant or ventricular assist device implant after their index MV-surgery were excluded from readmission quantification after the respective secondary procedure.

## 2.3. Echocardiographic Studies

Transthoracic and/or transesophageal echocardiographic data was performed at CUIMC and assessed for LVEF, left ventricular end-diastolic-diameter (LVEDD), MR, aortic insufficiency (AI) or aortic stenosis (AS), and tricuspid regurgitation (TR) for each patient. This data was assessed preoperatively, postoperatively with and without anesthesia, at a follow-up <6-months, 6 - 18-month (1-year) follow-up, and >18-month post-operation. Follow-up data was assessed for LVEF, LVEDD, MR, and changes in LVEF and LVEDD with respect to the preoperative values. Grading of MR and other valve disease (none/trace-0, mild-1, moderate-2, moderately-severe-3, severe-4) was based on standard guidelines for MR-quantification outlined by the American Society of Echocardiography (ASE) and the European Association of Echocardiography (EAE) [14]. Preoperative LVEDD-dilation severity was based off of recommended gender-stratified ranges from the EAE and ASE as outlined in **Supplemental Table S1** [15]. Only patients that had post-discharge follow-up echocardiographic studies were included in this analysis (n = 98 at <6 months; n = 93 at 1 year).

## 2.4. Statistical Analysis

Descriptive statistics were used to summarize patient demographics, medical/surgical histories, concomitant procedures, STS scores, and echocardiographic information. Categorical variables are presented by frequencies (n) and percentages (%). The differences between (MVR) and (MVR) were evaluated by chi-squared or Fisher's Exact tests for these variables. Mean  $\pm$  standard deviation (SD) or median (interquartile range) were used to summarize continuous variables.

Two-sample independent t-tests or the non-parametric equivalent—Wilcoxon Rank-Sum test—for skewed data were used to estimate the differences for such factors. Overall survival and time to readmission (all-cause and HF only) were estimated with the use of the Kaplan–Meier method and compared between groups by means of the log-rank test. Cox proportional hazards models were used to estimate the hazard ratios (HR: 95% CI).

Furthermore, due to the observational nature of the data, we employed several methods to account for confounding and create comparable risk groups in the MVR and MVr cohorts. Specifically, we fit and compared the results of the following approaches: 1) multivariable (adjusted) regression with stepwise selection, 2) propensity score approach with inverse probability weighting (IPW), and 3) univariable (unadjusted) regression. Standardized differences were calculated to compare patient features with respect to demographics, surgical/medical characteristics, concomitant procedures, and STS scores, with imbalance being defined as an absolute value greater than 0.10 (non-negligible effect size) [16]. All variables found to be imbalanced were used in the adjusted analysis approach 1) and in the propensity score analysis 2). The use of inverse probability weighting was preferred to pair matching and allowed the inclusion of the largest possible, however comparable, MVR and MVr cohorts. All statistical analyses were performed with SAS (v.9.4, SAS Institute, Inc., Cary, NC) using a type I error set at 0.05.

### 3. Results

#### 3.1. Baseline Characteristics

Baseline characteristics of the 263 MVr-patients and the 81 MVR-patients are outlined in **Table 1**. The patient groups were similar in most characteristics except LVEF, MR, TR, AI and history of CKD. On average, MVR-patients generally had higher LVEF than MVr-patients (median (IQR) 45 (35 - 55) vs. 37 (28 - 55);  $p = 0.004$ ). More MVR-patients had CKD (17.28% vs. 8.37%;  $p = 0.0219$ ), at least MR  $\geq 3$  (67.9% vs. 53.61%,  $p = 0.0231$ ), and TR  $\geq 3$  (17.28% vs. 5.7%;  $p = 0.001$ ). AI  $\geq 3$  was more prevalent in MVr patients (10.27% vs. 3.7%,  $p = 0.0467$ ). Other past medical history, New York Heart Association (NYHA), and non-heart valve comorbidities were not significantly different between groups (**Table 1**). Of the MVr cohort, 197 (73%) and 21 (8%) patients underwent repair with complete and partial annular rings respectively, whereas 50 (19%) patients underwent MVr without annular ring utilization. Ring sizes ranged from 24 mm to 36 mm: 24 mm ( $n = 5$ ), 26 mm ( $n = 57$ ), 27 mm ( $n = 2$ ), 28 mm ( $n = 118$ ), 29 mm ( $n = 1$ ), 30 mm ( $n = 27$ ), 31 mm ( $n = 1$ ), 32 mm ( $n = 6$ ), 36 mm ( $n = 1$ ). Of the MVR cohort, 14 (18%) patients received a mechanical valve whereas 62 (82%) patients received a bioprosthesis. Valve sizes ranged from 24 to 33 mm: 24 mm ( $n = 1$ ), 25 mm ( $n = 19$ ), 26 mm ( $n = 1$ ), 27 mm ( $n = 31$ ), 29 mm ( $n = 13$ ), 31 ( $n = 4$ ), 25/33 mm (On-X Valve;  $n = 7$ ). Out of the total 344 patients in this study, 5 (1%) were converted from MVr to MVR during their initial intervention due to

inadequate repair (these patients were analyzed in the replacement cohort).

As expected, 30-day-mortality scores for MVR were higher than MVr, highlighting the overall higher surgical risk associated with this cohort: (median (IQR) 6.29 (3.22 - 11.11) vs. 3.50 (1.85 - 5.74),  $p < 0.0001$ ) Additionally, predicted length-of-stay scores for MVR-patients were higher for stays longer than 14 days (median (IQR): 17.38 (12.44 - 27.73) vs. 12.31 (7.27 - 17.63),  $p < 0.0001$ ) and lower than for stays shorter than 6 days (median (IQR): 11.43 (5.63 - 18.31) vs. 18.09 (11.30 - 29.58),  $p < 0.0001$ ). MVR-patients scored higher than MVr for predicted risk of reoperation (13.36 (10.52 - 16.84) vs. 9.62 (7.59 - 12.15),  $p < 0.0001$ ).

### 3.2. Follow-Up Echocardiographic Data and MR-Recurrence

Echocardiographic baseline data was available from 199 out of the 344 patients ( $n = 153$  MVr;  $n = 46$  MVR). Within the echo cohort, MVR patients had a higher baseline EF (45% (35% - 55%) vs. 35% (24.4% - 45.7%),  $p = 0.001$ ) and a higher proportion of MR  $\geq 3$  (73.9% vs. 55.6%,  $p = 0.009$ ) (**Table 1**).

The data was divided into echocardiographic data taken at postoperative time points  $< 6$ -month ( $n = 98$ ; MVr = 75, MVR = 47) and 1-year ( $n = 93$ ; MVr = 75, MVR = 18). MR tended to be higher in the follow-ups of patients who underwent MVr who a higher recurrence of MR-grade  $\geq 2$  at both the  $< 6$ -month (15.9% vs. 0%) and the 1-year (29.5% vs. 4.3%) time points (**Table 2**).

Compared to baseline, at both  $< 6$ -month and 1-year follow-ups, LVEF increased in MVr patients but decreased in MVR patients: (mean (SD): 2.91 (11.9) vs. -6.39 (16.3),  $p = 0.02$ ) (2.39 (12) vs. -2.5 (8),  $p = 0.04$ ), respectively. LVEDD and LVEF were not significantly different between the two surgery groups at either follow-up (**Table 2**).

### 3.3. Survival

141 out of the 344 patients died during the entire observed time period of 16 years. 98 of these deaths occurred after any readmission (66 MVr and 32 MVR). Interestingly, the hazard ratio estimates generated by all three approaches 1) adjusted analysis, 2) propensity score IPW and 3) unadjusted analysis were comparable, indicating a good control of confounding imbalance between the two groups. Since one of our main goals was to make inferences on potential predictors of mortality and hospital readmission, in the sections below we focused mostly on the results generated by the adjusted models. Results from all three methods can be found in **Tables 3-6**.

Overall survival within the 16-year period survival was worse in MVR patients. Based on the adjusted analysis, the HR-adj was of 1.82 (95%CI) (1.05 - 3.16),  $p = 0.034$ ) (**Table 3**). Predictors of overall mortality included history of DM, CKD, or another concomitant cardiac procedure (**Table 3**).

A total of 78 (22.66%) subjects receiving MVr and 32 (39.51%) receiving MVR died within 5 years of their operation (**Figure 2**). Our analysis found no difference

**Table 2.** Comparison of echocardiographic data.

	MVr	MVR	P-value
<6 Months	N = 75	N = 23	
LVEF	36 (30 - 55)	47 (25 - 57)	0.76
ΔLVEF	2.91 (11.9)	-6.39 (16.3)	0.02*
	N = 67	N = 25	
LVEDD	5.2 (4.6 - 5.8)	5 (4.6 - 5.6)	0.59
ΔLVEDD	1.58 (2.73)	1.48 (2.25)	0.90
	N = 88	N = 30	
MR	0 (0 - 1)	0 (0 - 1)	0.09
MR 2+	14 (15.9)	0	
1 Year	N = 75	N = 18	
LVEF	37 (30 - 55)	42.5 (30 - 50)	0.90
ΔLVEF	2.39 (12)	-2.5 (8.0)	0.04*
	N = 65	N = 18	
LVEDD	5.3 (4.7 - 6)	5.3 (4.7 - 5.9)	0.72
ΔLVEDD	0.87 (2.53)	0.93 (2.32)	0.90
	N = 78	N = 23	
MR	1 (0 - 2)	0 (0 - 1)	0.06
MR 2+	23 (29.5)	1 (4.3)	

Data are presented as medians (interquartile range: IQR) and mean (SD) for mean (Δ) differences compared to baseline. \*Significant differences between MVr and MVR groups. Comparisons between the groups were assessed using the non-parametric test Wilcoxon Rank-Sum.

**Table 3.** Cox regression analysis for overall survival (OS).

	HR	95% CI	P-value
Unadjusted Analysis			
MVR vs MVr	1.58	(1.10, 2.27)	0.013*
Inverse Probability Weighting <sup>†</sup>			
MVR vs MVr	1.68	(1.22, 2.30)	0.001*
Adjusted/Multivariable Analysis <sup>§</sup>			
MVR vs MVr	1.82	(1.05, 3.16)	0.034*
Hx of DM	2.23	(1.32, 3.77)	0.003*
HX of CKD	2.50	(1.24, 5.05)	0.010*
CABG	2.57	(1.39, 4.73)	0.003*
AVR	4.28	(2.36, 7.76)	<0.0001*
TVR_r	3.72	(1.75, 7.92)	0.001*
Other_cardiac_proced	2.56	(1.48, 4.45)	0.001*

\*Significant differences between MVr and MVR groups. <sup>†</sup>Inverse probability of treatment weighting (IPTW) using the propensity score method. <sup>§</sup>Adjusted analysis used stepwise variable selection.

**Table 4.** Cox regression analysis for overall survival (OS), 5-year cutoff.

	HR	95% CI	P-value
Unadjusted Analysis			
MVR vs MVr	1.44	(0.95, 2.17)	0.082
Inverse Probability Weighting <sup>†</sup>			
MVR vs MVr	1.25	(0.88, 1.79)	0.221
Adjusted/Multivariable Analysis <sup>§</sup>			
MVR vs MVr	1.77	(0.98, 3.17)	0.057
Hx of DM	2.48	(1.41, 4.38)	0.002*
HX of CKD	2.97	(1.45, 6.12)	0.003*
CABG	2.22	(1.15, 4.26)	0.017*
AVR	4.21	(2.25, 7.89)	<0.0001*
TVR/r	3.64	(1.65, 8.06)	0.001*
Other cardiac proced	2.88	(1.59, 5.21)	0.001*

\*Significant differences between MVr and MVR groups. <sup>†</sup>Inverse probability of treatment weighting (IPTW) using the propensity score method. <sup>§</sup>Adjusted analysis used stepwise variable selection.

**Table 5.** Cox regression analysis for 5-year all-cause hospital readmission.

	HR	95% CI	P-value
Unadjusted Analysis			
MVR vs MVr	0.79	(0.53, 1.17)	0.247
Inverse Probability Weighting <sup>†</sup>			
MVR vs MVr	0.82	(0.62, 1.07)	0.138
Adjusted/Multivariable Analysis <sup>§</sup>			
MVR vs MVr	0.78	(0.46, 1.32)	0.355
LVEDD	1.48	(1.16, 1.90)	0.002*
HX of DM	1.96	(1.28, 3.01)	0.002*
HX of CKD Cr 2	2.43	(1.42, 4.14)	0.001*
CABG	0.42	(0.27, 0.66)	0.001*
TVR/r	0.43	(0.20, 0.94)	0.034*

\*Significant differences between MVr and MVR groups. <sup>†</sup>Inverse probability of treatment weighting (IPTW) using the propensity score method. <sup>§</sup>Adjusted analysis used stepwise variable selection.

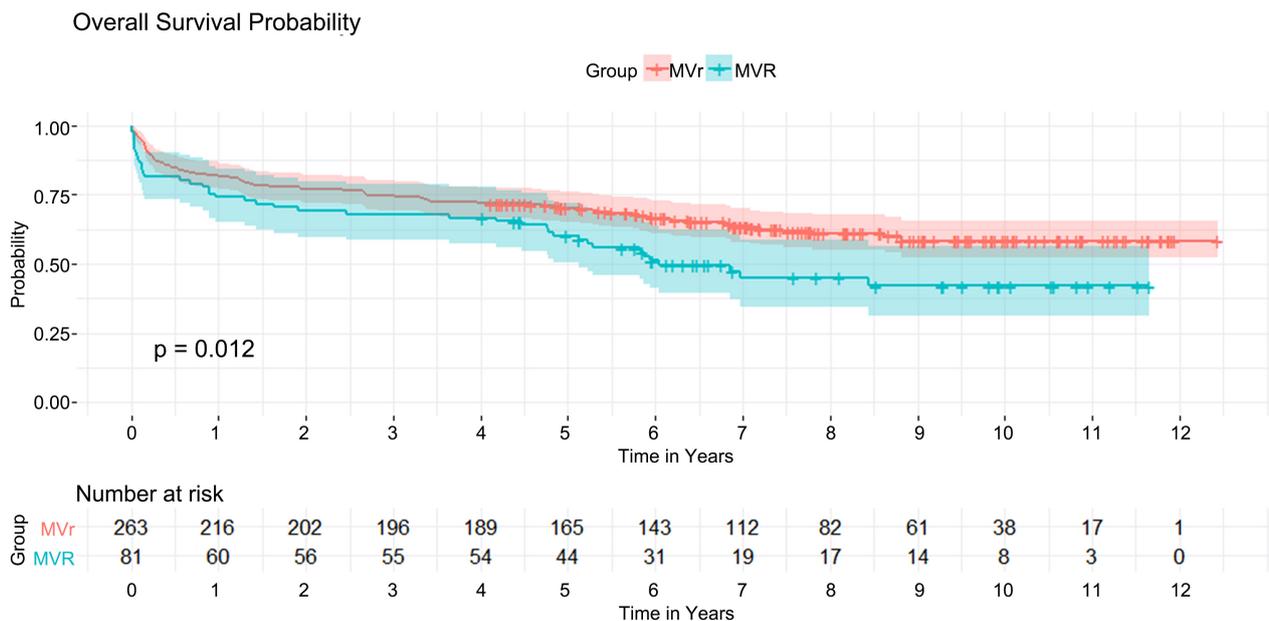
**Table 6.** Cox regression analysis for 5-year heart failure (HF) hospital readmission.

	HR	95% CI	P-value
Unadjusted Analysis			
MVR vs MVr	0.69	(0.40, 1.17)	0.167

**Continued**

Inverse Probability Weighting <sup>†</sup>			
MVR vs MVr	0.60	(0.41, 0.88)	0.008*
Adjusted/Multivariable Analysis <sup>§</sup>			
MVR vs MVr	0.52	(0.25, 1.09)	0.084
LVEDD	1.74	(1.31, 2.31)	0.002*
HX of DM	2.80	(1.62, 4.84)	0.002*
HX of CKD Cr 2	2.56	(1.33, 4.94)	0.005*
CABG	0.35	(0.20, 0.62)	0.003*
Gender (Male)	2.02	(1.14, 3.58)	0.016*

\*Significant differences between MVr and MVR groups. <sup>†</sup>Inverse probability of treatment weighting (IPTW) using the propensity score method. <sup>§</sup>Adjusted analysis used stepwise variable selection.

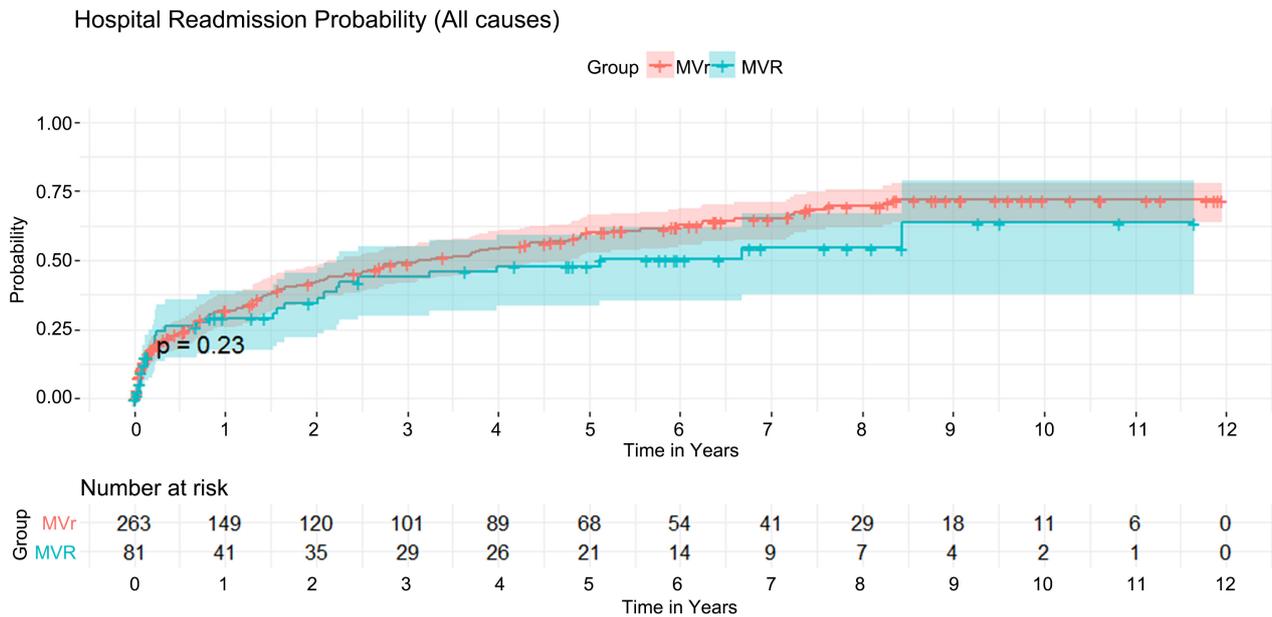


**Figure 2.** Overall survival probability curve.

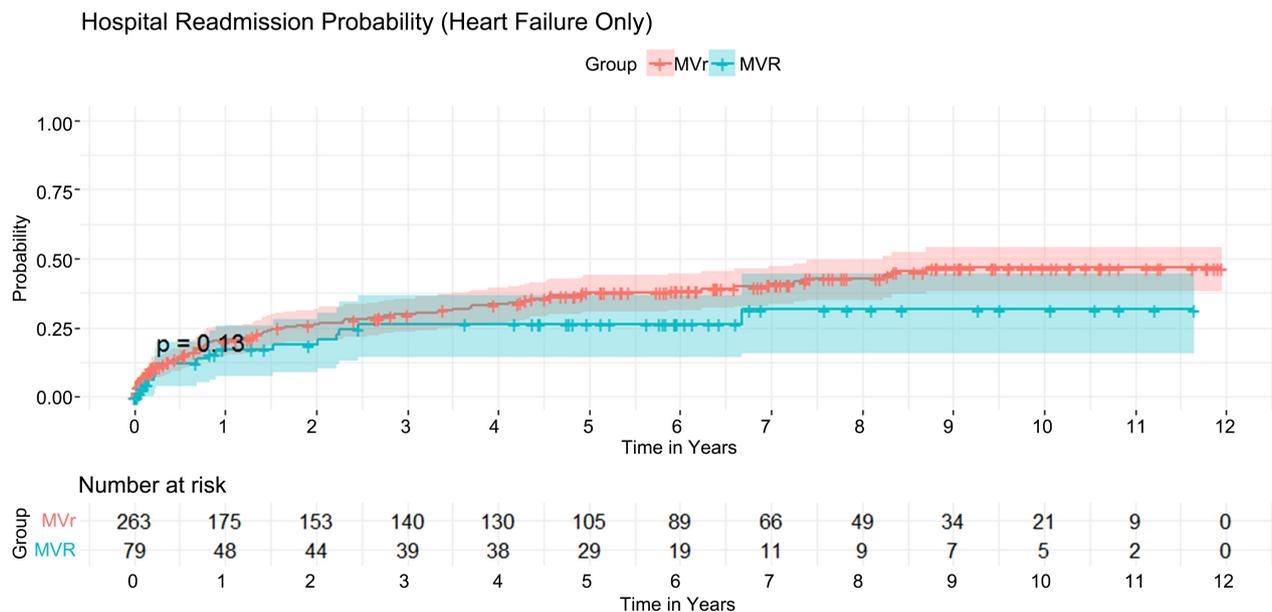
between the 2 groups at this time point ( $p = 0.06$ ). Significant predictors at this time point were the same as those in overall survival (**Table 4**).

**3.4. Readmission**

162 of 344 patients were readmitted within the study period with 297 readmissions of any cause (**Figure 3**). Although a greater percent of MVr patients were readmitted for any cause, all-cause readmission was not significantly different between MVr and MVR treatment groups: HR-adj 0.78 (0.46 - 1.32),  $p = 0.36$ ). Patients with diabetes, CKD, a higher LVEDD, or a concomitant CABG or TV procedure were more likely to be readmitted at any time after the initial intervention (**Table 5**).



**Figure 3.** Overall all-cause readmission curve.



**Figure 4.** Overall heart failure readmission curve.

Among the 297 readmissions, 178 were due to HF and occurred in 99 out of the 162 readmitted patients (**Figure 4**). MVR patients were less likely to be readmitted for HF within 5 years postop (HR-adj = 0.52 (0.25 - 1.09),  $p = 0.08$ ). Higher LVEDD (HR-adj = 1.74 (1.31 - 2.31),  $p < 0.001$ ), DM (HR-adj = 2.8 (1.62 - 4.84),  $p < 0.001$ ), CKD (HR-adj = 2.56 (1.33 - 4.94),  $p = 0.033$ ), and male gender (HR-adj = 2.02 (1.14, 3.58),  $p = 0.016$ ) were predictive of HF readmission 5 years after the index surgery (**Table 6**). Concomitant CABG was found to be protective (HR-adj = 0.35 (0.2 - 0.62),  $p < 0.001$ ) (**Table 6**).

### 3.5. Hospitalization

Length of hospitalization after surgery was significantly higher in the MVR group (13 (1.7 - 24.3) vs. 11 (2.2 - 19.8),  $p = 0.02$ ). The present study was consistent with STS-calculator predictions for differences between procedure groups in prolonged-admissions (43.2% vs. 30.8%,  $p = 0.039$ ), but contradicted the predicted differences in short-admissions (7.4% vs. 8.7%,  $p = 0.705$ ) (**Supplemental Table S2**).

The total number of readmissions of each patient after their index procedure was not found to be significantly different between the two procedure groups in the readmission cohort (2 (0 - 4) vs. 2 (0 - 7),  $p = 0.07$ ) (**Supplemental Table S2**). MV-reoperations occurred 15 times throughout the 13-year range of the study, all of which came after MVr; this constitutes 5.7% of the MVr cohort.

## 4. Discussion

The most effective surgical treatment for FMR remains unclear, which is reflected by the ambiguity of the 2017 AHA/ACC guidelines. Historically, a perceived correlation between lower surgical risk and longer postoperative survival existed for MVr over MVR, with a strong preference for retaining native leaflet tissue in a lower surgical risk procedure with MVr with the potential for longer-term survival. However, the associated complications resulting from both procedures have ultimately led to most FMR patients to be treated with more conservative therapies [10]. In the current study, we sought to determine if the type of surgery for FMR had an impact on hospital-readmission rate after surgery up to 5 years post-operatively. The primary findings were: 1) MVR-patients represent a sicker, higher-risk surgical population in this study based on the STS-score, 2) recurrence of MR was higher in MVr versus MVR within 6 and 1 months after surgery, 3) LVEF decreased amongst MVR patients as opposed to slightly increasing in MVr patients, 4) all-cause readmission was not significantly different between procedure groups, and 5) HF-readmission was markedly higher in MVr in comparison to MVR.

### 4.1. Primary Outcomes

The general consensus is to reserve MVR for the treatment of severe FMR if repair is not technically possible, but to perform MVr when ring annuloplasty can allow leaflet coaptation in all other cases. A Cardiothoracic Surgical Trials Network (CSTN) study beginning in 2014 evaluated the risks and compared the outcomes of MVR and MVr surgeries in FMR with or without concomitant CABG. Although this study found no discernable differences in survival at 2-year follow-up, moderate to severe recurrence was higher in MVr over MVR-patients (58.8% vs. 3.8%) and the rate of cardiovascular readmission became significantly higher in repair patients (48.3% vs. 32.2%), likely as a consequence of MR-recurrence [17]. This suggests that MVR confers a stabilizing effect to the cardiac geometry that slows geometric destabilization. Although the

recurrence of MR has been well established in the context of FIMR and annuloplasty repair, there is limited data regarding the recurrence of MR or long-term cardiac outcomes when treating FMR.

In the current study, our analysis did not identify procedure type as a risk factor for all-cause readmission. 30-day readmission in MVR and MVr groups was at 8.6% and 10.6% respectively, which are both lower than the previously reported values by Medicare study (22% & 26.4%). The heterogeneity of the patient population in this study with regard to comorbidities and concomitant procedures likely contribute to the wide variety of rehospitalizations amongst the groups. HF-readmission rates were consistently lower in the MVR group.

MR at follow-up was higher in MVr patients at every time point. This data correlates with the findings of previous studies and adds evidence to current reasoning that MVR confers a more durable protection from MR recurrence than MVr. The higher postoperative MR in MVr-patients likely explains the HF-readmission differences. Secondary MR, if left untreated, predisposes a patient to adverse cardiac events, especially HF. Although there were no significant differences in rates of early rehospitalization between the two populations, the differences in the rates of MR recurrence may reinitiate the cycle of FMR and subsequent HF in MVr-patients, thus escalating readmission by the 1-year mark. The COAPT trial by Stone *et al.* found that percutaneous MVr yielded improved survival and lower hospitalization rates within 2 years of the operation than medical therapy alone.

There has been renewed interest in the study of surgical outcomes after FMR. A recent study by Vassileva *et al.* quantified the readmission rates of Medicare patients receiving these treatments [18]. They found that preoperative HF was a major predictor for postoperative HF readmission in both MVr and MVR groups, but did not conclusively draw differences between the readmission rates of the two procedures. Hung *et al.* found that 70% of those receiving joint annuloplasty CABG procedures for moderate to severe MR had 3-4+ recurrent MR 1 - 5 years postop [19]. This data, finally, was conclusively studied in the CTSN trial of CABG vs. CABG + MVr for moderate-MR. In this study, 151 and 150 patients were studied in isolated CABG and CABG + MVr groups respectively, randomized to each treatment group. The addition of MVr produced no clinical benefit in terms of mortality nor did it produce reverse remodeling significantly different from CABG alone [9]. Collectively these data put into question the appropriateness of MVr in the treatment of FMR. The tendency towards recurrence after MVr is likely due to the continuous ventricular remodeling that occurs postoperatively. Therefore, in order to effectively treat FMR, these studies seem to suggest that reverse ventricular modeling must occur.

Since the observed remodeling metrics were not different between MVR and MVr in this study, the effect on ventricular remodeling was not adequately assessed. Regardless, it is important to note that LVEF difference between pre- and postoperative showed increased postoperative LVEF in the MVr group over the MVR group at follow-ups less than 6 months with a mean LVEF decrease in

MVR patients. This could be due to the use of non-chordal-sparing replacement, which has been associated with ventricular-decompensation and subsequently poor outcomes [20]. This may also contribute to HF readmission of MVR patients however this concept requires further validation.

LVEDD-dilation is indicative of progression to the later stages of dilated cardiomyopathy (DCM) and HF respectively. There is no previous data to reference our findings on the predictive value of LVEDD dilation on HF readmission, however there is similar data associating this variable with MR recurrence. Braun *et al.* reported that preoperative LVEDD size > 6.5 cm was a significant predictor of MR recurrence [21]. This similarity suggests a possible connection between MR recurrence and HF readmission in this patient population. Whether in the context of HF or MR recurrence, these findings demonstrate that intervention later in the progression of DCM or HF limits success and worsens prognosis. The present study demonstrates an association with MVr and a higher rate of HF rehospitalizations that is likely due to early MR recurrence. Our data correlating severe preoperative LVEDD dilation and HF-readmission suggests a decline in surgical effectiveness that coincides with DCM progression; this relationship may be elucidated by future studies. Nevertheless, this investigation demonstrates the ineffectiveness of MVr to stabilize ventricular geometry that results in pathological recurrence and HF-readmission.

#### 4.2. Future Directions

Our study revealed trade-offs between MVr and MVR in treating FMR that preclude identification of a superior procedure. MVR could provide an opportunity to stably correct secondary MR, but increased risk of postoperative complications and mortality are significant drawbacks. Since patients in this study were beholden to criteria that indicate surgery later in the disease process, it stands to reason that earlier intervention could bypass potential complications and prevent further irreversible changes to cardiac geometry.

Minimally-invasive percutaneous procedures offer a possible solution to surgical complications. Additionally, the normally less stringent criteria of percutaneous procedures vs open surgeries could make this therapeutic option available to lower risk patients earlier in the progression of the disease. The primary concern of percutaneous valve interventions is the stability of the correction [22]. However recent studies have shown that the efficacy of percutaneous MVr is comparable to classic repair procedures when treating FMR [23]. The COAPT trial by Stone *et al.* found that percutaneous MVr yielded improved survival and lower hospitalization rates than medical therapy alone within 24 months of the procedure [24]. The success of percutaneously deployed valves has been established in aortic valve replacement and the ineffectiveness of current methods to treat FMR necessitates a novel method; a minimally-invasive MVR procedure could be beneficial to treat FMR to both minimize potential surgical complications and provide long-term correction. Longer term follow-up will help determine the durability of these types of repairs.

### 4.3. Limitations

The present study has several limitations inherent to the retrospective design. Data collected is limited to what is available in the patient-database, and there were a percentage of patients with incomplete discharge data that did not allow for analysis. It is not clear if these patients represent a different risk strata of patients than those analyzed, or if their outcomes would have affected our analysis. Although patients included in this study were primarily followed at the NewYork-Presbyterian Hospital System, readmission at other institutions is possible, though this was documented in subsequent clinic visits in many cases. Additionally, the patients are largely heterogeneous in terms of concomitant procedures, procedure types, and comorbidities. This precludes adequate analysis of isolated MV procedures and may mask true associations and differences. In addition, there are large differences in risk between the two groups which complicate evaluation of survival data. As this was not the primary objective of the study, we reserve conclusions to recurrence of MR and hospital readmission. Further, multiplicity was not addressed in this study due to its exploratory nature and the presented P-values are therefore not adjusted for multiple comparisons. Finally, this study examines FMR on a broader scope and does not assess ischemic and non-ischemic differences.

Treatment selection in our study was due to surgeon discretion and methods for how specific procedural decisions were made are consequently unknown and likely non-homogeneous. Furthermore, factor selection was based on previously identified factors or criteria that may influence our outcomes. Consequently, this implies that our IPTW model should only be used to identify binary differences rather than a precise effect size.

### 5. Conclusion

The burden of FMR is growing, and inadequate treatment leads to readmissions and rising health care costs. Despite high readmission rates in both FMR patient groups, HF readmission occurs more frequently for MVr than MVR patients. MR is not the only causal factor for HF, however, a higher rate of recurrence suggests that MVr may be inadequate in treating FMR. Future focused studies are needed to effectively explore specific risk factors that lead to MR recurrence and fully define anatomical criteria for effective, durable repair techniques in FMR.

### Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

### References

- [1] Braunschweig, F., Cowie, M.R. and Auricchio, A. (2011) What Are the Costs of Heart Failure? *EP Europace*, **13**, ii13-ii17. <https://doi.org/10.1093/europace/eur081>
- [2] Grigioni, F., Enriquez-Sarano, M., Zehr, K.J., Bailey, K.R. and Tajik, A.J. (2001) Ischemic Mitral Regurgitation: Long-Term Outcome and Prognostic Implications with Quantitative Doppler Assessment. *Circulation*, **103**, 1759-1764.

- <https://doi.org/10.1161/01.CIR.103.13.1759>
- [3] Trichon, B.H., Felker, G.M., Shaw, L.K., Cabell, C.H. and O'Connor, C.M. (2003) Relation of Frequency and Severity of Mitral Regurgitation to Survival among Patients with Left Ventricular Systolic Dysfunction and Heart Failure. *The American Journal of Cardiology*, **91**, 538-543. [https://doi.org/10.1016/S0002-9149\(02\)03301-5](https://doi.org/10.1016/S0002-9149(02)03301-5)
- [4] Hillis, G.S., Moller, J.E., Pellikka, P.A., Bell, M.R., Casaclang-Verzosa, G.C. and Oh, J.K. (2005) Prognostic Significance of Echocardiographically Defined Mitral Regurgitation Early after Acute Myocardial Infarction. *American Heart Journal*, **150**, 1268-1275. <https://doi.org/10.1016/j.ahj.2005.01.020>
- [5] Persson, A., Hartford, M., Herlitz, J., Karlsson, T., Omland T and Caidahl, K. (2010) Long-Term Prognostic Value of Mitral Regurgitation in Acute Coronary Syndromes. *Heart*, **96**, 1803-1808. <https://doi.org/10.1136/hrt.2010.203059>
- [6] Nishimura, R.A., Otto, C.M., Bonow, R.O., Carabello, B.A., Erwin, J.P., Fleisher, L.A., Jneid, H., Mack, M.J., McLeod, C.J., O'Gara, P.T., Rigolin, V.H., Sundt, T.M., and Thompson, A. (2017) 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*, **135**, e1159-e1195. <https://doi.org/10.1161/CIR.0000000000000503>
- [7] Bolling, S.F., Pagani, F.D., Deeb, G.M. and Bach, D.S. (1998) Intermediate-Term Outcome of Mitral Reconstruction in Cardiomyopathy. *The Journal of Thoracic and Cardiovascular Surgery*, **115**, 381-388. [https://doi.org/10.1016/S0022-5223\(98\)70282-X](https://doi.org/10.1016/S0022-5223(98)70282-X)
- [8] Crabtree, T.D., Bailey, M.S., Moon, M.R., Munfakh, N., Pasque, M.K., Lawton, J.S., Moazami, N., Aubuchon, K.A., Al-Dadah, A.S. and Damiano Jr., R.J. (2008) Recurrent Mitral Regurgitation and Risk Factors for Early and Late Mortality after Mitral Valve Repair for Functional Ischemic Mitral Regurgitation. *The Annals of Thoracic Surgery*, **85**, 1537-1543. <https://doi.org/10.1016/j.athoracsur.2008.01.079>
- [9] Smith, P.K., Puskas, J.D., Ascheim, D.D., Voisine, P., Gelijns, A.C., Moskowitz, A.J., Hung, J.W., Parides, M.K., Ailawadi, G., Perrault, L.P., Acker, M.A., Argenziano, M., Thourani, V., Gammie, J.S., Miller, M.A., Page, P., Overbey, J.R., Bagiella, E., Dagenais, F., Blackstone, E.H., Kron, I.L., Goldstein, D.J., Rose, E.A., Moquete, E.G., Jeffries, N., Gardner, T.J., O'Gara, P.T., Alexander, J.H. and Michler, R.E., for the Cardiothoracic Surgical Trials Network Investigators (2014) Surgical Treatment of Moderate Ischemic Mitral Regurgitation. *The New England Journal of Medicine*, **371**, 2178-2188. <https://doi.org/10.1056/NEJMoa1410490>
- [10] Goel, S.S., Bajaj, N., Aggarwal, B., Gupta, S., Poddar, K.L., Ige, M., Bdair, H., Anab-tawi, A., Rahim, S., Whitlow, P.L., Tuzcu, E.M., Griffin, B.P., Stewart, W.J., Gillinov, M., Blackstone, E.H., Smedira, N.G., Oliveira, G.H., Barzilai, B., Menon V and Kapadia, S.R. (2014) Prevalence and Outcomes of Unoperated Patients with Severe Symptomatic Mitral Regurgitation and Heart Failure: Comprehensive Analysis to Determine the Potential Role of MitraClip for This Unmet Need. *Journal of the American College of Cardiology*, **63**, 185-186. <https://doi.org/10.1016/j.jacc.2013.08.723>
- [11] Kaneko, T., Cohn, L.H. and Aranki, S.F. (2013) Tissue Valve Is the Preferred Option for Patients Aged 60 and Older. *Circulation*, **128**, 1365-1371. <https://doi.org/10.1161/CIRCULATIONAHA.113.002584>
- [12] Nishimura, R.A., Otto, C.M., Bonow, R.O., Carabello, B.A., Erwin, J.P., Guyton, R.A., O'Gara, P.T., Ruiz, C.E., Skubas, N.J., Sorajja, P., Sund, T.M. and Thomas, J.D. (2014) 2014 AHA/ACC Guideline for the Management of Patients with Valvular

- Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology*, **63**, e57-e185. <https://doi.org/10.1016/j.jacc.2014.02.536>
- [13] Acker, M.A., Parides, M.K., Perrault, L.P., Moskowitz, A.J., Gelijns, A.C., Voisine, P., Smith, P.K., Hung, J.W., Blackstone, E.H., Puskas, J.D., Argenziano, M., Gammie, J.S., Mack, M., Ascheim, D.D., Bagiella, E., Moquete, E.G., Ferguson, T.B., Horvath, K.A., Geller, N.L., Miller, M.A., Woo, Y.J., D'Alessandro, D.A., Ailawadi, G., Dagenais, F., Gardner, T.J., O'Gara, P.T., Michler, R.E. and Kron, I.L. (2014) Mitral-Valve Repair versus Replacement for Severe Ischemic Mitral Regurgitation. *The New England Journal of Medicine*, **370**, 23-32. <https://doi.org/10.1056/NEJMoa1312808>
- [14] Grayburn, P.A., Weissman, N.J. and Zamorano, J.L. (2012) Quantitation of Mitral Regurgitation. *Circulation*, **126**, 2005-2017. <https://doi.org/10.1161/CIRCULATIONAHA.112.121590>
- [15] Lang, R.M., Badano, L.P., Mor-Avi, V., Afilalo, J., Armstrong, A., Ernande, L., Flachskampf, F.A., Foster, E., Goldstein, S.A., Kuznetsova, T., Lancellotti, P., Muraru, D., Picard, M.H., Rietzschel, E.R., Rudski, L., Spencer, K.T., Tsang, W. and Voigt, J.U. (2015) Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *European Heart - Journal Cardiovascular Imaging*, **16**, 233-270. <https://doi.org/10.1093/ehjci/jev014>
- [16] Austin, P.C. (2011) An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behavioral Research*, **46**, 399-424. <https://doi.org/10.1080/00273171.2011.568786>
- [17] Goldstein, D., Moskowitz, A.J., Gelijns, A.C., Ailawadi, G., Parides, M.K., Perrault, L.P., Hung, J.W., Voisine, P., Dagenais, F., Gillinov, A.M., Thourani, V., Argenziano, M., Gammie, J.S., Mack, M., Demers, P., Atluri, P., Rose, E.A., O'Sullivan, K., Williams, D.L., Bagiella, E., Michler, R.E., Weisel, R.D., Miller, M.A., Geller, N.L., Taddei-Peters, W.C., Smith, P.K., Moquete, E., Overbey, J.R., Kron, I.L., O'Gara, P.T. and Acker, M.A. (2016) Two-Year Outcomes of Surgical Treatment of Severe Ischemic Mitral Regurgitation. *The New England Journal of Medicine*, **374**, 344-353. <https://doi.org/10.1056/NEJMoa1512913>
- [18] Vassileva, C.M., Ghazanfari, N., Markwell, S., Boley, T. and Hazelrigg, S. (2014) Preoperative Heart Failure in the Medicare Population Undergoing Mitral Valve Repair and Replacement: An Opportunity for Improvement. *The Journal of Thoracic and Cardiovascular Surgery*, **148**, 1393-1399. <https://doi.org/10.1016/j.jtcvs.2013.12.010>
- [19] Hung, J., Papakostas, L., Tahta, S.A., Hardy, B.G., Bollen, B.A., Duran, C.M. and Levine, R.A. (2004) Mechanism of Recurrent Ischemic Mitral Regurgitation after Annuloplasty: Continued LV Remodeling as a Moving Target. *Circulation*, **110**, II85-II90. <https://doi.org/10.1161/01.CIR.0000138192.65015.45>
- [20] Schmitto, J.D., Lee, L.S., Mokashi, S.A., Bolman, R.M., Cohn, L.H. and Chen, F.Y. (2010) Functional Mitral Regurgitation. *Cardiology in Review*, **18**, 285-291. <https://doi.org/10.1097/CRD.0b013e3181e8e648>
- [21] Braun, J., van de Veire, N.R., Klautz, R.J., Versteegh, M.I., Holman, E.R., Westenberg, J.J., Boersma, E., van der Wall, E.E., Bax, J.J. and Dion, R.A. (2008) Restrictive Mitral Annuloplasty Cures Ischemic Mitral Regurgitation and Heart Failure. *The Annals of Thoracic Surgery*, **85**, 430-437. <https://doi.org/10.1016/j.athoracsur.2007.08.040>
- [22] George, J.C., Varghese, V., Dangas, G. and Feldman, T.E. (2011) Percutaneous Mi-

tral Valve Repair: Lessons from the EVEREST II (Endovascular Valve Edge-to-Edge Repair Study) and Beyond. *JACC Cardiovascular Interventions*, **4**, 825-827. <https://doi.org/10.1016/j.jcin.2011.05.010>

- [23] Feldman, T., Fernandes E and Levisay, J.P. (2018) Transcatheter Mitral Valve Repair/Replacement for Primary Mitral Regurgitation. *Annals of Cardiothoracic Surgery*, **7**, 755-763. <https://doi.org/10.21037/acs.2018.07.04>
- [24] Stone, G.W., Lindenfeld, J., Abraham, W.T., Kar, S., Lim, D.S., Mishell, J.M., Whisenant, B., Grayburn, P.A., Rinaldi, M., Kapadia, S.R., Rajagopal, V., Sarembock, I.J., Brieke, A., Marx, S.O., Cohen, D.J., Weissman, N.J. and Mack, M.J. (2018) Transcatheter Mitral-Valve Repair in Patients with Heart Failure. *The New England Journal of Medicine*, **379**, 2307-2318. <https://doi.org/10.1056/NEJMoa1806640>

### Supplemental Table

**Supplemental Table S1.** Echocardiographic Metrics—MR grading and LVEDD reference ranges based on ASE & EAE guidelines.

MR Grading		
None/Trace		0
Mild		1
Moderate		2
Moderately-Severe		3
Severe		4
LVEDD Ranges (cm)		
	Women	Men
Normal-Range	3.9 - 5.3	4.2 - 5.9
Mildly-Abnormal	5.4 - 5.7	6.0 - 6.3
Moderately-Abnormal	5.8 - 6.1	6.4 - 6.8
Severely-Abnormal	≥6.2	≥6.9

MR indicates mitral regurgitation; LVEDD, left ventricular end diastolic diameter.

**Supplemental Table S2.** Hospitalization Data

	MVr		MVR		P-value
	Median/N	IQR/%	Median/N	IQR/%	
Length-of-Stay (Primary Admission) <sup>‡</sup>	11	8.8	13	11.3	0.017*
Prolonged-Admission (>14 Days)	81	30.8	35	43.2	0.039*
Short-Admission (<6 Days)	23	8.7	6	7.4	0.705
Times Readmitted <sup>†</sup>	2	2	2	5	0.07
MV Reoperations	15	5.7	N/A	N/A	N/A

\*Significant difference between MVr and MVR groups; †, within readmission cohort (N = 163); ‡, median and interquartile range presented; IQR, interquartile range.