Predictors of hospital mortality after surgery for ischemic mitral regurgitation

Abdelsalam Elhenawy[1], Khaled Algarni[1], Vivek Rao[1], and Terrence Yau[1]

[1]University Health Network

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Abstract

BACKGROUND: The benefit of mitral valve repair over replacement in patients with ischemic mitral regurgitation is still controversial. We report our early postoperative outcomes of repair versus replacement. METHODS: Data were collected for patients undergoing first-time mitral valve surgery for ischemic mitral regurgitation between 1990 and 2009 (n = 393). Patients who underwent combined procedures for papillary muscle rupture, post-infarction ventricular septal defect, endocarditis, or any previous cardiac surgery were excluded. Preoperative demographics, operative variables, and hospital outcomes were analyzed, and multivariable regression analysis was employed to identify independent predictors of hospital mortality. RESULTS: Valve repair was performed in 42% (n=164) of patients and replacement in 58% (n=229). Patients who underwent replacement were older and had a higher prevalence of unstable angina, New York Heart Association class IV symptoms, preoperative cardiogenic shock, preoperative myocardial infarction, peripheral vascular disease, renal failure, and urgent or emergency surgery (all $p < 0.05$). Unadjusted hospital mortality was higher in patients undergoing valve replacement (13% versus 5%, $p = 0.01$). Valve repair was associated with a lower prevalence of postoperative low cardiac output syndrome. Multivariable analysis revealed that age, urgency of operation, and preoperative left ventricular function were independent predictors of hospital mortality. Importantly, mitral valve repair versus replacement was not an independent predictor of hospital mortality. CONCLUSION: Our data did not suggest an early survival benefit to mitral valve repair over replacement for ischemic mitral regurgitation. However, age, left ventricular dysfunction, and the need for urgent surgery were independently associated with hospital mortality.

Predictors of hospital mortality after surgery for ischemic mitral regurgitation

Running head: **ischemic mitral regurgitation surgery**

Abdelsalam M. Elhenawy[1,2] MD, MSc (Surg), MSc (Epi), PhD. E-mail, a_elhenawy@hotmail.com Khaled Algarni[1] MD, MHSc. E-mail, khaledga999@hotmail.com Vivek Rao[1] MD, PhD. E-mail, vivek.rao@uhn.ca Terrence M. Yau[1] MD, MSc. E-mail, terry.yau@uhn.ca

[1]Division of Cardiovascular Surgery, Peter Munk Cardiac Centre, University Health Network, Toronto, Ontario, Canada.

[2]Division of Cardio-thoracic Surgery, Al Azhar University, Cairo, Egypt.

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Address correspondence to: Dr. Elhenawy, PhD, Edmonton, AB, T6J 2E4 Canada. Tel: 780.200.6771

Abbreviations and Acronyms

IMR: ischemic mitral regurgitation

LV: left ventricular

MVR: mitral valve replacement

MVr: mitral valve repair

MV: mitral valve

RCT: randomized controlled trial

MR: mitral regurgitation

CABG: coronary artery bypass grafting

VSD: ventricular septal defect

LCOS: low cardiac output syndrome

IABP: intra-aortic balloon pump

NYHA: New York Heart Association

CPB: cardiopulmonary bypass

OR: Odds Ratio

LVEF: left ventricular ejection fraction

CTSN: Cardiothoracic Surgical Trials Network

Abstract

BACKGROUND:

The benefit of mitral valve repair over replacement in patients with ischemic mitral regurgitation is still controversial. We report our early postoperative outcomes of repair versus replacement.

METHODS:

Data were collected for patients undergoing first-time mitral valve surgery for ischemic mitral regurgitation between 1990 and 2009 (n = 393). Patients who underwent combined procedures for papillary muscle rupture, post-infarction ventricular septal defect, endocarditis, or any previous cardiac surgery were excluded. Preoperative demographics, operative variables, and hospital outcomes were analyzed, and multivariable regression analysis was employed to identify independent predictors of hospital mortality.

RESULTS:

Valve repair was performed in 42% (n=164) of patients and replacement in 58% (n=229). Patients who underwent replacement were older and had a higher prevalence of unstable angina, New York Heart Association class IV symptoms, preoperative cardiogenic shock, preoperative myocardial infarction, peripheral vascular disease, renal failure, and urgent or emergency surgery (all $p < 0.05$). Unadjusted hospital mortality was higher in patients undergoing valve replacement (13% versus 5%, $p = 0.01$). Valve repair was associated with a lower prevalence of postoperative low cardiac output syndrome.

Multivariable analysis revealed that age, urgency of operation, and preoperative left ventricular function were independent predictors of hospital mortality. Importantly, mitral valve repair versus replacement was not an independent predictor of hospital mortality.

CONCLUSION:

Our data did not suggest an early survival benefit to mitral valve repair over replacement for ischemic mitral regurgitation. However, age, left ventricular dysfunction, and the need for urgent surgery were independently associated with hospital mortality.

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Introduction

Ischemic mitral regurgitation (IMR) is a frequent complication of coronary artery disease, which is associated with increased left ventricular (LV) dysfunction and mortality [1, 2]. Most experts in mitral surgery advocate for concomitant correction of more than moderate IMR during coronary bypass surgery. However, the choice of mitral valve repair (MVr) or mitral valve replacement (MVR) is controversial [3-5]. Mitral valve repair has been associated with lower hospital mortality and greater late survival compared to replacement in patients with degenerative mitral valve disease [6, 7]. In contrast, the benefits of mitral valve (MV) repair compared to replacement in patients with IMR are not as well defined. Several retrospective studies suggested lower operative mortality and better long-term survival with repair compared to replacement in patients with IMR [8-15]. However, these studies are largely limited by inherent selection bias in favor of repair. Indeed, a recent randomized controlled trial (RCT) [16], which compared MV repair versus replacement in patients with IMR showed equivalent operative mortality and short-term survival but better freedom from recurrent mitral regurgitation (MR) with MV replacement. The purpose of this study is to compare mortality and major morbidities after MV repair or replacement for IMR while accounting for all known confounders using rigorous regression methodology with validation of multivariable analysis by bootstrapping, and evaluation of the regression model for discrimination, calibration, and multicollinearity.

Patients and Methods

Data Collection and Study Outcomes

Our institutional review board approved this study and access to clinical data. We reviewed our institutional database that prospectively captures clinical and laboratory data on all patients who underwent first time MV surgery for IMR with or without coronary artery bypass grafting (CABG) between January 1, 1990, and December 31, 2009. After exclusion of all patients who underwent combined mitral valve procedures (except for atrial septal defect closure, tricuspid valve surgery, or MAZE procedure) and any patient who had echocardiographic evidence of structural (chordal or leaflet) mitral valve disease, a ruptured papillary muscle, post-infarction ventricular septal defect (VSD), left ventricular (LV) aneurysm, or endocarditis, we identified 393 patients. Of these patients, 164 (42%) had MVr, and 229 (58%) had MVR.

Preoperative demographics, operative variables, and postoperative outcomes were retrospectively analyzed, and multivariable regression analysis was employed to identify independent predictors of hospital mortality. Importantly, to validate the diagnosis of IMR, we conducted a detailed chart review to exclude any patient with evidence of structural (chordal or leaflet) disease of the MV, which included all preoperative cardiac imaging tests within a month of surgery, as well as the operative records and pathology reports, to exclude any patients with congenital, degenerative, rheumatic or infective mitral valve pathology.

The primary outcome was 30-day mortality. Secondary endpoints include low cardiac output syndrome (LCOS), stroke, acute kidney injury, and myocardial infarction (MI). LCOS was defined as the need for either postoperative intra-aortic balloon pump (IABP) support or sustained high-dose inotropic support. The need for inotropic support was defined as the use of epinephrine, dobutamine, milrinone, or dopamine to keep cardiac output greater than 2.2 $L/min/m^2$ after optimizing preload and afterload and correction of all electrolyte and blood gas abnormalities.

Analysis

Statistical analysis was performed with SAS 9.2 software (SAS Institute, Inc, Cary, NC). Categorical variables were expressed as percentages. Continuous variables were expressed as means $\pm$ standard deviations. We analyzed categorical variables with chi-square analysis, or if there were few outcomes, Fisher's exact test was used. Continuous variables that had a normal distribution were analyzed using the Student's t-test, and variables that had non-normal distribution were analyzed using the Wilcoxon rank-sum test. Statistical significance was based on two-sided p-values less than 0.05.

Variables with a univariate p-value of less than 0.25 and those of known biological importance were selected for inclusion in a multivariable logistic regression model to identify independent predictors of hospital mortality. Model discrimination and calibration were evaluated by the area under the receiver operating characteristic curve (C statistic), and the Hosmer–Lemeshow goodness-of-fit statistic, respectively. In the current study, a model's discrimination with an area under the ROC curve greater than 0.7 was considered a good model, and Hosmer–Lemeshow test with $P > 0.05$ indicates a well-calibrated model. To validate the final predictive model, we did bootstrap replication with 1000 re-samples.

Results

Demographics and Baseline Clinical Profile

Preoperative patient characteristics are detailed in Table 1**.** Patients who underwent MVR were overall a sicker group of patients; they were older, were more likely to have unstable angina, New York Heart Association (NYHA) class IV symptoms, cardiogenic shock, recent MI, peripheral vascular disease, end-stage renal failure and the need for urgent or emergent surgery. These differences were not unexpected since the patients were not randomized. The decision whether to repair or replace the mitral valve was based at least in part on these characteristics.

Operative Details and Hospital Outcomes

Operative details are presented in **Table 2** . Most patients (93%) had concomitant CABG, and 4% underwent concomitant tricuspid valve surgery. In the replacement group, 72% of the patients had chordal preservation. In the repair group, a rigid or semirigid ring was used to achieve a downsizing annuloplasty. Patients who underwent MVR had longer cardiopulmonary bypass (CPB) and cross-clamp times ($p < 0.0001$). Hospital outcomes are summarized in **Table 3** . Patients who underwent MV replacement had a higher rate of LCOS with an increased requirement for inotropic ($p = 0.01$) and IABP support ($p < 0.0001$). These differences were associated with significantly higher unadjusted mortality in the MV replacement cohort.

Observed Mortality and Postoperative Outcomes

Table 3 indicates that the 30-day mortality rate was higher ($p = 0.01$) in the MVR group, consistent with their increased preoperative risk profile (**Table 1).** In patients undergoing replacement, the prevalence of sepsis ($p = 0.03$), pulmonary complications ($p = 0.0008$), and surgical re-exploration ($p = 0.04$), was higher than in the repair group. There was no difference between groups concerning perioperative MI, pacemaker insertion, atrial fibrillation, acute kidney injury, sternal wound infection, or permanent neurological events (**Table 3).** However, MVR patients had significantly higher resource utilization, including higher duration of mechanical ventilation ($p < 0.0001$), longer intensive care unit stay ($p = 0.03$), and hospital stay ($p < 0.0001$) than the repair group (**Table 3).**

Predictors of Mortality

Multivariable analysis (**Table 4)** identified the following variables as independent predictors of mortality: 1) age (Odds Ratio [OR] = 1.05, per 5-year increment), the need for urgent/emergent surgery (OR = 5.46) and left ventricular ejection fraction (LVEF) < 40% (OR = 2.14). Surgical procedure (repair vs. replacement) was not an independent predictor of mortality. The 30-day mortality predictors were internally validated using a 1000-resampling bootstrap procedure that showed the stability of the results (**Table 5**). Moreover, there were no features of multicollinearity, as the standard errors of the affected coefficients were relatively small (**Table 5**). The c-statistic for this multivariable model was 0.80, with asymptotic 95% confidence of 0.75-0.86, indicating good discrimination of the model (**Table 6 and Figure 1).** The Hosmer-Lemeshow ^{2} statistic showed that the model goodness of fit was good ($x^2 = 2.78$, $p = 0.95$), indicating good predictive performance (discrimination and calibration) of the derived model.

Discussion

In patients with IMR, the current ACC/AHA practice guidelines do not specify whether to repair or replace the mitral valve to treat severe IMR [17]. In reality, the decision to repair or replace the mitral valve depends

on multiple factors, including the clinical presentation and patient comorbidities. While mitral repair for IMR usually comprises an undersized ring annuloplasty, the decision with regards to technique may also be influenced, particularly, when there is more complex pathology (severe tethering, basal aneurysm/or dyskinesis, coaptation depth greater than 10 mm, or a markedly dilated left ventricle), by the "repairability" of the valve, which is in part dependent on the surgeon's experience in mitral valve repair. The controversy over the relative benefits and risks of mitral repair in this challenging patient population have led some surgeons to consider chordal-sparing mitral valve replacement as the most conservative approach to minimize the risk of early or late failure of valve repair. This strategy is supported by a randomized controlled trial conducted by the Cardiothoracic Surgical Trials Network (CTSN) which reported no difference in LV reverse remodeling or survival either at 12 months [16], or at 24 months [18] between patients who had mitral valve repair and those who underwent chordal-sparing mitral valve replacement. However, the recurrence of either moderate or severe mitral regurgitation was considerably higher in the repair group than in the replacement group (32.6% vs. 2.3%, P<0.001 at 12 months [16] and 58.8% vs. 3.8%, P<0.001 at 24 months [18]). While mortality did not differ between groups in the CTSN trial, the trial was not powered to detect differences in survival. In contrast, a recent meta-analysis that included this CTSN trial [19] and previous five meta-analyses [20-24] reported lower 30-day mortality associated with MVr compared to MVR.

Likewise, our findings are in line with multiple retrospective studies [8-10, 12], which have suggested higher mortality with MVR compared to MVr.

The observed hospital mortality of MVR and MVr in our study (5.8% and 13.3% for repair and replacement groups, respectively) are comparable to those reported by Grossi et al. (10% and 20%) [13] Milano et al. (6.3% and 18.9%) [14], and Magne et al. (9.7% and 17.4%) [15], for repair and replacement groups, respectively, in a similar era. Gillinov et al. [8] reported a 13% overall 30-day mortality (both repair and replacement) in all patients undergoing surgery for IMR, which is comparable to our overall 30-day mortality (10%). A report from the Society of Thoracic Surgeons (STS) database [25] which included 26,463 patients undergoing MVR/MVr + CABG operations between mid-2011 and mid-2014 reported mortality rates of 4.9% and 8.7% for repair and replacement with CABG, respectively, indicating a continued improvement in early survival outcomes with time.

In our study, mortality was predicted by urgent surgery, LVEF less than 40%, and age. Thourani and associates [9] reported increasing age (OR 1.53 per 10-year increments in age), urgent (OR 3.03) and emergent surgery (OR 9.18), and mitral valve replacement (OR 1.72) as independent predictors of mortality. Similarly, Maltais et al. [28] reported that redo surgery (hazard ratio = 3.39; P < .001) age (hazard ratio = 1.5; P = 0.03), urgent or emergent surgery (hazard ratio = 2.08; P = 0.007) and low LVEF (hazard ratio = 1.31; P = 0.026) were the only independent predictors of one-year survival. In this study, the performance of mitral valve repair versus replacement did not affect survival.

Moreover, data from both randomized trials [16] and observational studies [29] have noted a higher rate of recurrent mitral regurgitation with mitral valve repair, and recurrent MR of moderate or greater severity has been independently associated with worse long-term outcomes [29]. However, improved late survival after MVr has been reported both by a retrospective study [10] and a meta-analysis of nine studies, despite significant rates of recurrent mitral regurgitation after repair. Nevertheless, we believe that the decision between MVr and a chordal-sparing MVP may be best decided based on individual patient demographics, anatomic factors, and the surgeon's experience.

Our study has several strengths. First, previous observational studies are limited by the inclusion of some patients with nonischemic mitral regurgitation. In our study, we rigorously reviewed the preoperative recent cardiac imaging, pathology reports, and operative notes to verify a purely ischemic etiology. Second, all data were prospectively collected by a single independent, experienced operator. Therefore, the probability of selection, information, or ascertainment bias is reduced. Third, we had very low missing data (<1%) for all variables collected in the database. Because this study focused on short-term (30-day) operative outcomes, loss to follow-up was not an issue. The main limitation of our study is the lack of long-term survival and echocardiography data. However, our primary aim was to compare short-term hospital outcomes between

MVr and MVR in patients with IMR.

Conclusion

Our results suggest that hospital mortality after surgery for ischemic mitral regurgitation is determined mostly by the patient's risk profile rather than the choice of valve repair or replacement. Valve repair may reduce the risk of postoperative low cardiac output syndrome. However, the decision to repair or replace the valve should consider the preoperative risk profile and physiological reserve of each patient as well as the surgeon's experience in mitral valve repair.

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Table 1. Preoperative variables

Variable	**MVr (n = 164)**	**MVR (n = 229)**	P-value
Age (years)	64.02 ± 9.27	67.66 ± 9.09	<0.0001
Body surface area (m^2)	1.86 ± 0.23	1.84 ± 0.22	0.4
Female gender	50 (30)	31 (36)	0.2
Hypertension	105 (63)	139 (61)	0.6
Hyperlipidemia	129 (79)	123 (55)	<0.0001
Diabetes mellitus	53 (32)	51 (22)	0.03
History of smoking	118 (72)	154 (68)	0.4
Unstable angina	51 (31)	122 (54)	<0.0001
LVEF < 40 %	92 (56)	119 (52)	0.4
NYHA Class IV symptoms	67 (41)	136 (60)	0.0003
Stroke/TIA	18 (8)	25 (11)	0.3
COPD	10 (6)	26 (11)	0.07
CHF	119 (73)	182 (80)	0.1
Cardiogenic shock	3 (2)	36 (16)	<0.0001
MI within 30 days	32 (20)	73 (32)	0.006
PVD	25 (15)	59 (26)	0.01
Renal dialysis	4 (2)	18 (8)	0.02

Variable	**MVr (n = 164)**	**MVR (n = 229)**	P-value
Urgent/emergent surgery	73 (45)	138 (61)	0.002

Continuous variables are presented as means ± standard deviation; categorical variables are presented as number (%).

LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; TIA = transient ischemic attack; COPD = chronic obstructive pulmonary disease; PVD = peripheral vascular disease; CHF = congestive heart failure; MI = myocardial infarction. ***Table 2. Peri-operative profile***

Variable	**MVr (n = 164)**	**MVR (n = 229)**	P-value
Concomitant CABG	154 (94)	211 (92)	0.5
Tricuspid valve surgery	8 (5)	8 (3)	0.5
MAZE procedure	1 (1)	2 (1)	0.8
Atrial septal defect closure	7 (4)	15 (7)	0.3
Cardiopulmonary bypass time (min)	120.9 ± 32.65	147.7 ± 43.79	<0.0001
Cross clamp time (min)	96.84 ± 26.18	114.0 ± 35.69	<0.0001
Intra-aortic balloon pump.	12 (7)	58 (25)	<0.0001
Inotropes	108 (66)	176 (78)	0.01
Low cardiac output syndrome.	17 (10)	49 (22)	0.003

Continuous variables are presented as means ± standard deviation; categorical variables are presented as number (%).

CABG = coronary artery bypass grafting.

Table 3. Hospital Outcomes

Variable	**MVr (n = 164)**	**MVR (n = 229)**	*P-value*
Peri-operative myocardial infarction	5 (3)	1 (0.5)	0.08
Postoperative pacemaker insertion	21 (13)	24 (11)	0.5
Postoperative atrial fibrillation	44 (27)	46 (20)	0.1
Acute kidney injury	5 (3)	14 (6)	0.2
Superficial and deep sternal infection	2 (1)	11 (5)	0.1
Sepsis	5 (3)	19 (8)	0.03
Re-exploration	9 (5)	26 (11)	0.04
Pulmonary complication	22 (13)	63 (28)	0.0008
Post-operative persistent neurologic defect	3 (2)	3 (1)	0.3
Mortality	9 (5)	30 (13)	0.01
Ventilation (hours)	42.05 ± 159.3	83.27 ± 196.6	<0.0001
Intensive care unit (ICU) stay (hours)	105.4 ± 212	220 ± 1014	0.03
Hospital stay (days)	10.93 ± 10.08	18.01 ± 21.27	<0.0001

Continuous variables are presented as means ± standard deviation; categorical variables are presented as number (%).

Table 4. Odds ratio estimates for predictors of mortality in ischemic mitral regurgitation groups excluding cardiopulmonary bypass time

Variable	β Coefficient	Point estimate (Odds Ratio = Exp. of β)	Standard Error	Significance	95% Confidenc
Age*	0.049	1.050	0.021	0.018	1.008 - 1.093
Urgent surgery	1.697	5.460	0.358	< 0.0001	2.709 - 11.003
LVEF <40%	0.761	2.140	0.368	0.039	1.040 - 4.401
Constant	-6.413	0.002	1.481	< 0.0001	

Exp. = exponent; Sig. =significance; LVEF = left ventricular ejection fraction.

**Odds ratio is per 5-year increment in age.*

Table 5. Bootstrap estimates for predictors of mortality in ischemic mitral regurgitation groups excluding cardiopulmonary bypass time

Variable	β Coefficient	Bootstrap	Bootstrap	Bootstrap	Bootstrap	Bootstrap
		Bias	Standard Error	Sig. (2-tailed)	95% Confidence interval (β) Lower	95% Confider Upper
Age*	0.049	0.003	0.022	0.023	0.013	0.100
Urgent surgery	1.697	0.036	0.395	0.001	0.938	2.466
LVEF <40%	0.761	0.053	0.382	0.033	0.069	1.623 -
Constant	-6.413	-0.275	1.544	0.001	-10.167	-3.952

LVEF = left ventricular ejection fraction.

**Odds ratio is per 5-year increment in age.*

Table 6. Predicted probability using the area under the curve

Area	Standard Error[a]	Asymptotic Significance[b]	Asymptotic 95% Confidence Interval	Asymptotic 95% Confidence I
			Lower Bound	Upper Bound
0.79	0.038	< 0.0001	0.75	0.86

The test result variable(s): Predicted probability has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

1. Under the nonparametric assumption
2. Null hypothesis: true area = 0.5

Figure legends

Figure 1: Receiver operating characteristics curve and the area under the curve for the sensitivity and specificity values of the prediction model.