Journal of the American Heart Association

ORIGINAL RESEARCH

Increased Mortality in Patients With Preoperative and Persistent Postoperative Pulmonary Hypertension Undergoing Mitral Valve Surgery for Mitral Regurgitation: A Cohort Study

Michael V. Genuardi, MD, MS*; Daniel Shpilsky, MD*; Adam Handen, MS; Gabrielle VanSpeybroeck, MD; Ann Canterbury, MD; Michael Lu, MD; Kayle Shapero, MD, PhD; Ricardo A. Nieves, MD; Floyd Thoma, BS; Suresh R. Mulukutla, MD; João L. Cavalcante, MD; Stephen Y. Chan, MD, PhD

BACKGROUND: Preoperative pulmonary hypertension (PH) is associated with excess mortality among patients with severe mitral regurgitation undergoing mitral valve surgery (MVS). However, the links between PH phenotype, pulmonary vascular remodeling, and persistent postoperative PH are not well understood. We aimed to describe the associations between components of pulmonary hemodynamics as well as postoperative residual PH with longitudinal mortality in patients with severe mitral regurgitation who received MVS.

METHODS AND RESULTS: Patients undergoing MVS for severe mitral regurgitation from 2011 to 2016 were retrospectively identified within our health system (n=488). Mean pulmonary artery pressure and other hemodynamic variables were determined by presurgical right-heart catheterization. Postoperative pulmonary artery systolic pressure was assessed on echocardiogram 42 to 365 days post-MVS. Longitudinal survival over a mean 3.9 years of follow-up was evaluated using Cox proportional hazards modeling to compare survival after adjustment for demographics, surgical characteristics, and comorbidities. Pre-MVS prevalence of PH was high at 85%. After adjustment, each 10-mm Hg increase in preoperative mean pulmonary artery pressure was associated with a 1.38-fold increase in risk of death (95% CI, 1.13–1.68). Elevated preoperative pulmonary vascular resistance, transpulmonary gradient, and right atrial pressure were similarly associated with increased mortality. Among 231 patients with postoperative echocardiogram, evidence of PH on echocardiogram (pulmonary artery systolic pressure ≥35 mm Hg) was associated with increased risk of death (hazard ratio [HR], 2.02 [95% CI, 1.17–3.47]); however, this was no longer statistically significant after adjustment (HR, 1.55 [95% CI, 0.85–2.85]).

CONCLUSIONS: In patients undergoing MVS for mitral regurgitation, preoperative PH, and postoperative PH were associated with increased mortality.

Key Words: mitral regurgitation ■ mitral valve surgery ■ mortality ■ pulmonary hypertension

Mitral regurgitation (MR) is the most common valvular disease for adults of all ages in the United States.[1] Left untreated, severe MR leads to worsening heart failure, hospitalization, and death.[2–4] Mitral valve surgery (MVS) is the third most commonly performed cardiac surgery in the United States,

Correspondence to: Michael V. Genuardi, MD, MS, Perelman Center for Advanced Medicine, University of Pennsylvania, 3400 Civic Center Blvd, 11th Floor South Pavilion, Philadelphia, PA 19104. E-mail: michael.genuardi@pennmedicine.upenn.edu or Stephen Y. Chan, MD, PhD, Center for Pulmonary Vascular Biology and Medicine, Pittsburgh Heart, Lung, Blood, and Vascular Medicine Institute, Pittsburgh, PA. Division of Cardiology, Department of Medicine, University of Pittsburgh School of Medicine and UPMC, 200 Lothrop Street BST-E1240, Pittsburgh, PA 15213. E-mail: chansy@pitt.edu

Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.018394

*Dr Genuardi and Dr Shpilsky contributed equally to this work.

For Sources of Funding and Disclosures, see page 12.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- In this large study of patients undergoing mitral valve surgery for severe mitral regurgitation, we show that pre- and postoperative pulmonary hypertension is associated with increased risk of death.
- Pulmonary hypertension is associated with increased risk of death irrespective of many clinical and surgical characteristics.

What Are the Clinical Implications?

- Risk stratification prior to surgery for severe mitral regurgitation should consider pulmonary hemodynamics more closely.
- There may be a role for earlier intervention for mitral valve surgery prior to the development of significant pulmonary hypertension; this would be an area for further investigation.

Nonstandard Abbreviations and Acronyms

mPAP	mean pulmonary artery pressure
MR	mitral regurgitation
MVS	mitral valve surgery
PASP	pulmonary artery systolic pressure
PCWP	pulmonary capillary wedge pressure
PH	pulmonary hypertension
TPG	transpulmonary gradient

behind coronary artery bypass grafting and aortic valve replacement.[5,6] The development of pulmonary hypertension (PH) with longstanding MR has been well described and is generally a poor prognostic sign.[7–10] In the surgical population specifically, previous studies have reported a worse prognosis with respect to mitral valve intervention in patients with severe mitral stenosis and concomitant pulmonary hypertension.[11–13] Similarly, long-term survival is decreased in patients with severe aortic stenosis and pulmonary hypertension undergoing surgical or transcatheter aortic valve intervention.[14–17] However, in contrast to mitral stenosis and aortic stenosis, much less is known about the relation between abnormal pulmonary hemodynamics and outcomes in patients with MR undergoing surgery.

Prior studies have reported that preoperative PH is associated with worse outcomes, but studies have been limited by sample size or noninvasive assessment of preoperative pulmonary artery pressures, limiting interpretation of hemodynamics and PH phenotypes.[18–20] Accordingly, previous analyses have focused on systolic pulmonary pressures alone and have not investigated the clinical significance of other right-sided hemodynamic findings. Finally, the relation between postoperative hemodynamics and PH reversibility with mortality has not been established.

Current American Heart Association/American College of Cardiology valvular heart disease guidelines have listed a class IIa (level of evidence: B) indication for MVS in asymptomatic patients with chronic, severe nonrheumatic primary MR when PH (defined as pulmonary artery systolic pressure >50 mm Hg) is present.[6] The decision to recommend MVS for patients with severe MR is ultimately a calculation between predicted benefit and potential harm; thus, detailed study of a high-risk group such as patients with PH undergoing MVS is essential.

We designed the present study to investigate the associations between preoperative hemodynamics and postoperative outcomes in patients undergoing MVS for severe MR. We aimed to describe the relative importance of various invasive hemodynamic parameters on postoperative survival and, additionally, to investigate the implication of persistent postoperative PH on long-term survival.

METHODS

Study Design, Setting, and Patients

We conducted a retrospective cohort analysis of patients undergoing MVS for severe MR within the University of Pittsburgh Medical Center, a large, multihospital health system in Pennsylvania encompassing over 40 hospitals. The primary exposures were PH before and after MVS. The primary outcome was post-MVS all-cause mortality.

Adult patients (aged ≥18 years) undergoing MVS at the 5 hospitals within the system performing this procedure between January 1, 2011 and June 30, 2016 were identified from an institutional databank used for quality improvement and outcomes reporting. We included only patients who had a right-heart catheterization available for review between 365 days and 1 day prior to MVS. Physician reviewers (D.S., G.V., and A.C.) determined the indication for surgery on the basis of operative reports and clinical data from the electronic health record. Only patients with either a primary or coprimary surgical indication of severe MR were included. Patients with both primary and secondary or functional MR were included. We excluded patients with concurrent severe mitral stenosis as well as patients without follow-up data.

This study was approved by the University of Pittsburgh Institutional Review Board. Specific informed consent was waived because of the retrospective

nature of the study and the determination of minimal risk to study patients. Because of the sensitive nature of the data collected for this study, requests to access the data set and analysis code for reasons of reproducibility and data integrity made by qualified researchers trained in human subject confidentiality may be sent to the corresponding authors.

Hemodynamic Measurements and PH Definitions

We identified preoperative hemodynamics and PH status on the basis of right-heart catheterization hemodynamic data obtained between 365 days and 1 day prior to MVS. All right-heart catheterizations were done during the course of routine clinical care and performed by experienced operators with patients supine and at rest. The right atrial, right ventricular, pulmonary artery, and pulmonary capillary wedge pressures (PCWP) were measured and recorded, and the cardiac output and index were calculated. The mean pulmonary artery pressure (mPAP) was determined by digitized waveform analysis. The cardiac output was based on either the indirect Fick method or thermodilution at the discretion of the operator. The average of both measurements was used when both were reported. Transpulmonary gradient (TPG) was calculated as PCWP–mPAP. The pulmonary vascular resistance (PVR) was calculated as TPG divided by the cardiac output. Dichotomous PH was defined as a mPAP >20 mm Hg as recommended on the basis of the recent 6th World Symposium on Pulmonary Hypertension guidelines.[21] We additionally defined 5 categories based on pulmonary hemodynamics, again according to recent recommendations:

1. No PH: mPAP ≤20 mm Hg;
2. Postcapillary PH: mPAP >20 mm Hg, PVR <3 Wood units, PCWP >15 mm Hg;
3. Precapillary PH: mPAP >20 mm Hg, PVR ≥3 Wood units, PCWP ≤15 mm Hg;
4. Combined pre-/postcapillary PH: mPAP >20 mm Hg, PVR ≥3 Wood units, PCWP >15 mm Hg;
5. Borderline/indeterminate PH: mPAP 20 to 25 mm Hg, PVR <3 Wood units, PCWP ≤15 mm Hg.

To screen for persistent PH after MVS, we then identified patients with echocardiograms obtained between 42 and 365 days after MVS. We elected to not include echocardiograms obtained prior to postoperative day 42 to allow for postoperative remodeling to occur and to broadly align with current societal recommendations for postsurgical imaging.[22,23] Postoperative PH was defined by either an estimated pulmonary artery systolic pressure (PASP) ≥35 mm Hg or a peak tricuspid regurgitant jet velocity >2.8 m/s, based on guidelines.[24] No postoperative PH determination was made in patients who had an echocardiogram but who did not have quantification of either PASP or tricuspid regurgitant jet velocity reported.

Clinical Variables and Follow-up

Variables such as demographics (age, sex, and body mass index), clinical laboratories, procedural characteristics, echocardiographic findings, and comorbidities were determined and entered into the database by clinicians at the time of MVS. Missing data were retrospectively added by physician reviewers if available from the patient chart. Determination of mortality was made by either query of the Social Security Death Index or by notification of death in the health system's electronic record, with last follow-up occurring on September 30, 2018, at which point surviving patients were censored.

Outcomes such as atrial fibrillation, myocardial infarction, stroke, infection, and renal failure during the postoperative period were defined as occurring during the same hospitalization as MVS. Immediate postoperative outcomes were assessed by physician review of the records from the hospitalization and outpatient notes, as appropriate. Postoperative death was defined as death occurring during index hospitalization or up to 30 days postoperatively, whichever was longer, in accordance with the usual Society for Thoracic Surgeons definition. Causes of death during the entire follow-up period were determined based on physician review of the patients' charts.

Statistical Analysis

We compared the baseline characteristics and postoperative outcomes between patients with and without preoperative PH by Student *t* test for continuous variables or χ^2 test for categorical variables. We used Wilcoxon rank sum tests for cases of variables with significant right skew (e.g., postoperative duration of ventilation, length of intensive care unit stay, and interval between MVS and echocardiography or right-heart catheterization).

We used Kaplan-Meier survival analysis to compare postoperative mortality between patients with and without preoperative PH, between patients with and without postoperative PH, and among patients with the different PH phenotypes. A log-rank test was used to compare survival, with *P*-value adjustment to maintain constant false discovery rate in the case of multiple comparisons using R package "survminer" (v0.4.4).[25] The independent association of PH with survival was then assessed with a Cox proportional hazards model to describe risk of mortality conditional on covariates. Three models were created for mPAP treated both continuously and dichotomously (divided at mPAP >20 mm Hg). Model 1 was adjusted

for days between catheterization and MVS as well as surgeon; Model 2, for days between catheterization and MVS, surgeon, age, sex, and body mass index; and Model 3, for Model 2 covariates plus type of mitral valve surgery (repair or replacement), cause of mitral regurgitation (primary versus secondary), concomitant aortic valve surgery, concomitant tricuspid valve surgery, concomitant coronary artery bypass grafting, diabetes mellitus, hypertension, prior clinical heart failure, preoperative ejection fraction, serum creatinine, platelet count, and albumin. When adjusting for surgeon, operators with fewer than 20 cases in the cohort were combined into a low-volume dummy variable for ease of modeling. The proportional hazards assumption was formally tested for each model by examination of the correlation between survival time and scaled Schoenfeld residuals for both the exposure of interest and the global model. None showed evidence of violation of the proportional hazards assumption.

To illustrate the association between hemodynamic parameters and post-MVS survival, we created 4 Cox survival models: mPAP, pulmonary vascular resistance, transpulmonary gradient, and right atrial pressure. We estimated survival at 3 years postoperatively for a range of each hemodynamic parameter, modeled as restricted cubic splines. All models were adjusted for a limited set of covariates (age, sex, and body mass index), and prediction models were standardized to a male patient of cohort average age and body mass index to make interpretation more intuitive. In the case of right atrial pressure, we intended to examine the isolated association of right ventricular filling pressure; thus, we additionally adjusted for PCWP, also modeled using a restricted cubic spline.

To assess for the association between postoperative PH and mortality, we compared post-MVS mortality for patients with and without postoperative PH via Kaplan-Meier analysis and log-rank test. We then compared survival for patients with preoperative PH who did not have PH postoperatively (reversed PH), patients with persistent PH postoperatively (persistent PH), and those with no preoperative PH. In the latter group, we included patients who did not have a postoperative echocardiogram and those with nondiagnostic PASP evaluations so as to provide a conservative analysis. After testing of the proportional hazards assumption and finding no evidence for violation for each presented model, mortality was compared for patients with and without postoperative PH both continuously and categorically using a series of 3 models, identical to the above except that time between MVS and echocardiogram replaced time between catheterization and MVS as a covariate.

All multivariable models were complete case analyses. Patient observations with and without missing variables were compared, in order to screen for systematic missingness (Table S1). Analyses were performed using R v3.6.0 (R Foundation for Statistical Computing, Vienna, Austria). Two-sided α=0.05 was set as the statistical significance threshold for all tests.

RESULTS

A total of 600 adult patients were identified having undergone MVS and having a right-heart catheterization between 365 and 1 day prior to MVS from a pool of 1935 total mitral valve surgeries performed during the study period at included institutions. We then excluded 39 patients whose primary or coprimary indication for surgery was not severe MR and 3 patients with unique indications for MVS (2 in the context of a complex congenital heart disease surgery and 1 in the setting of acute papillary muscle rupture post–myocardial infarction). Another 65 patients were excluded because of concomitant severe mitral stenosis. Five patients had no follow-up data and were excluded, making the final analytical cohort 488 patients (Figure 1). Among all 488 patients, the average (SD) age was 67.2 years (11.2 years), and 44.9% were women.

Among the 488 included patients, 413 (85%) had PH based on invasive hemodynamics; of these, 61 had mPAP >20 and <25 mm Hg. The baseline characteristics of the cohort according to preoperative PH status is shown in Table 1. There were significant differences between the groups, with patients with PH being older, having higher body mass index, and higher prevalence of several comorbidities including diabetes mellitus and dyslipidemia. Preoperative right-heart catheterization was performed a median (interquartile range) of 9 days (3–38 days) prior to surgery. Patients with PH had surgery sooner after the catheterization. Although a Society of Thoracic Surgeons risk score was not calculable for all procedure types included in this study (eg, combined dual-valve surgery or combined MVS and Maze), patients with PH had a significantly higher predicted operative mortality. Patients with PH were also more likely to undergo mitral valve replacement, rather than repair (Table 2). Selected postoperative outcomes of interest are also shown; patients with preoperative PH were noted to have a significantly longer ventilation time and intensive care unit stay.

Postoperative echocardiography was performed a median (interquartile range) of 93 days (63–192 days) after MVS, with no difference in timing between patients with and without preoperative PH (Table 3). On postoperative echocardiogram, patients with preoperative PH had slightly lower ejection fraction and higher pulmonary artery pressure. Of patients with

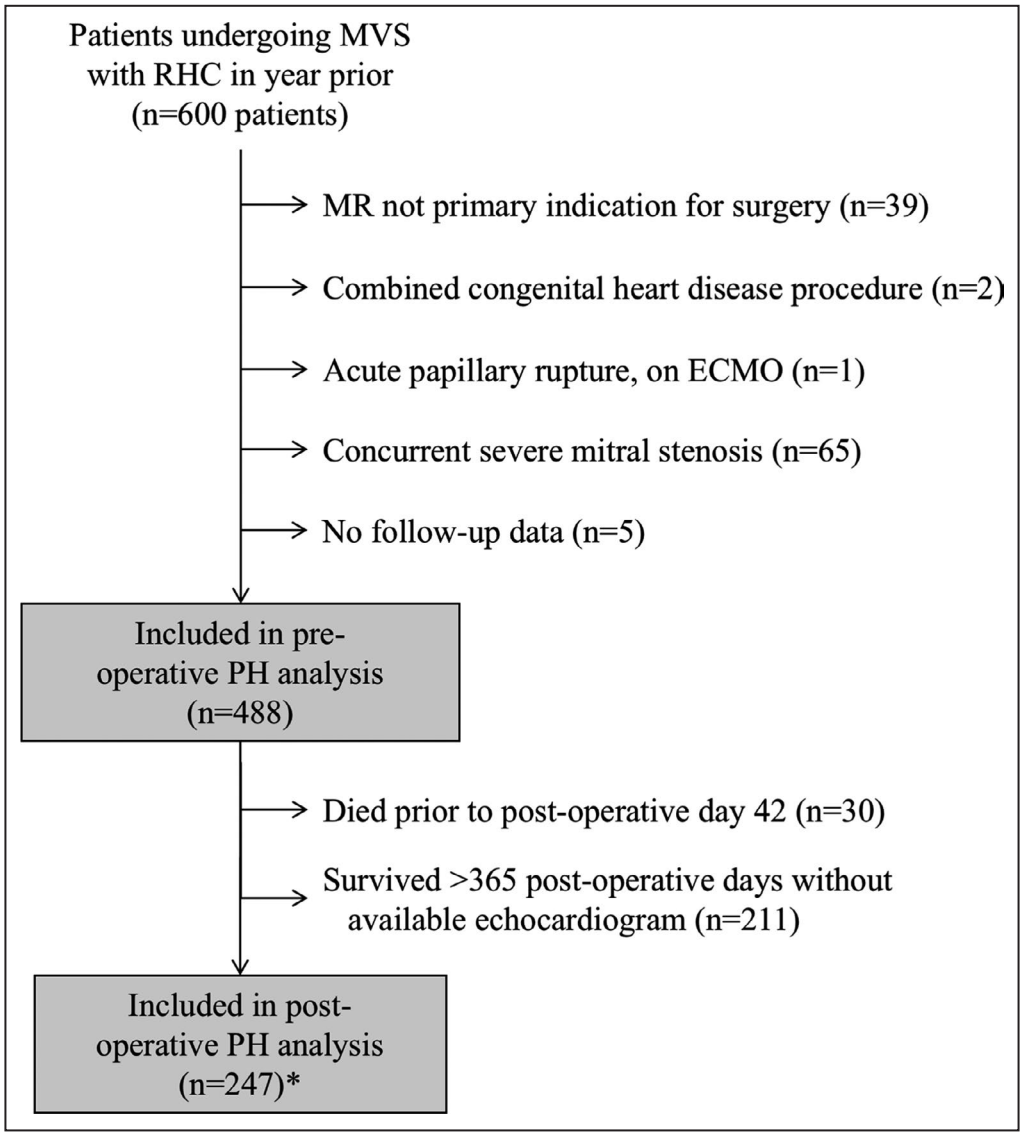


Figure 1. Study flow diagram.
*Includes 24 patients with nondiagnostic echocardiograms and 16 patients who died during the eligibility period of 42 to 365 days post-MVS and did not have a postoperative echocardiogram. ECMO indicates extracorporeal membrane oxygenation; MR, mitral regurgitation; MVS, mitral valve surgery; PH, pulmonary hypertension; and RHC, right-heart catheterization.

preoperative PH, 40% no longer had evidence of PH by the time of the echocardiogram. Right ventricular size and function were not substantially different between those with and without preoperative PH; however, there was a large proportion of missing right ventricular parameters.

There were 134 deaths after an average (SD) follow-up time of 3.9 years (2.0 years). Causes of death were able to be adjudicated in 55% of cases (Table S2). Death attributable to cardiovascular causes was most common (52%) among adjudicated cases, with death attributable to heart failure the most common reason for cardiovascular death. Notably, none of the 8 deaths in the no-PH group were attributable to cardiovascular causes, but only 2 of 8 deaths in this group were able to be adjudicated based on available records. Survival between groups differed greatly by pre-MVS presence of PH; the cumulative incidence of death per 100 patient-years was 2.3 (95% CI, 1.0–4.5) in the no-PH group and 8.1 (95% CI, 6.8–9.7) in the PH group. The Society of Thoracic Surgeons defined operative mortality in the no-PH and PH groups as 2.4% and 5.4%, respectively. These figures were similar to the risk algorithm-predicted mortality (P=1.0 and P=0.75, respectively). There were also significant survival differences after stratification by PVR and PH phenotype (Figure 2). When overall survival was analyzed for mPAP divided into 3 strata (<20, 20–25,

Table 1. Baseline Characteristics by Presence of Preoperative Pulmonary Hypertension

	Preoperative mPAP ≤20 mm Hg, N=75	Preoperative mPAP >20 mm Hg, N=413	*P* Value*
Age, y	64.1 (9.3)	67.7 (11.4)	0.01
Female, %	40.0%	45.8%	0.38
Body mass index, kg/m^2	26.0 (4.7)	28.4 (5.8)	0.0008
NYHA classification†			<0.0001
1	5.7%	1.0%	
2	34.3%	11.3%	
3	48.6%	47.9%	
4	11.4%	39.8%	
Preoperative ejection fraction, %	53.6 (11.3)	48.2 (14.5)	0.002
Diabetes mellitus, %	16.0%	31.2%	0.008
Hypertension, %	70.7%	79.9%	0.09
Dyslipidemia, %	56.0%	70.2%	0.02
Cerebrovascular disease, %	17.3%	24.5%	0.23
Dialysis, %	0%	4.1%	0.09
Current smoking, %	10.7%	18.4%	0.13
Days from catherization to surgery‡	23 (7–57)	8 (3–24)	0.002
Mean right atrial pressure, mm Hg	3.7 (2.3)	10.3 (5.5)	<0.0001
Mean pulmonary artery pressure, mm Hg	16.5 (2.4)	34.7 (9.2)	<0.0001
Mean pulmonary capillary wedge pressure, mm Hg	9.9 (3.8)	22.3 (7.3)	<0.0001
Pulmonary vascular resistance, Wood units	1.3 (0.8)	2.8 (1.9)	<0.0001
Cardiac output, L/min	5.4 (1.3)	4.8 (1.3)	0.001
Cardiac index, L/min per m^2	2.8 (0.6)	2.5 (0.6)	<0.0001
Hematocrit, %	38.9 (6.0)	36.4 (5.4)	0.0002
Platelets, 10^9 L^{-1}	201.7 (60.9)	195.2 (71.6)	0.46
Serum creatinine, μmol/L†	77.3 (19.7)	94.4 (67.0)	0.053
Serum albumin, g/L	38.6 (5.0)	35.7 (5.4)	<0.0001
Primary mitral regurgitation	73.3%	48.2%	<0.0001
Significant tricuspid regurgitation, moderate or greater	17.3%	32.9%	0.008
Calculated STS risk of mortality, %§	1.5 (1.9)	6.2 (7.2)	<0.0001

Values presented are column percentages for categorical variables or mean (SD) for continuous variables, except where otherwise noted; see below. mPAP indicates mean pulmonary artery pressure; NYHA, New York Heart Association; and STS, Society of Thoracic Surgeons.

*Result of *t* test or rank sum test where median and interquartile range are reported.

†NYHA functional status classification had a 29.5% missing data rate, and serum creatinine had a 19.3% missing rate; all other presented variables were under 4% missing.

‡Reported as median (interquartile range) because of right skew.

§Because of patients undergoing combined procedures, STS risk of mortality was calculable for 55% of the pulmonary artery pressure ≤20-mm Hg group and 40.7% of the pulmonary artery pressure >20-mm Hg group.

and ≥25 mm Hg), pairwise comparisons were significantly different between the mPAP <20-mm Hg and ≥25-mm Hg groups (*P*<0.001) and between the mPAP 20- to 25-mm Hg and ≥25-mm Hg groups (*P*=0.02). Survival was similar between the mPAP <20-mm Hg and 20- to 25-mm Hg groups (*P*=0.23) (Figure 2B). Pairwise comparisons between PH phenotype groups showed that compared with the no-PH group, increased mortality was observed among patients with postcapillary PH, precapillary PH, and combined pre- and postcapillary PH (all *P*<0.001). Mortality in patients with postcapillary PH and precapillary PH were statistically different (*P*=0.02), but mortality in combined PH versus postcapillary PH and combined PH versus precapillary PH were not (*P*=0.35 and *P*=0.09, respectively) (Figure 2D). Associations of postoperative complications and choice of mitral valve repair versus replacement with mortality are explored in Data S1 and Figures S1 and S2.

In a multivariable model accounting for timing of catheterization, surgeon, age, sex, body mass index, and all clinical covariates, each 10-mm Hg increase in mPAP was associated with a 38% increase in the risk of death (hazard ratio [HR], 1.38; 95% CI, 1.13–1.68) (Table 4). When modeled continuously using cubic spline functions and after adjustment, increases in

Table 2. Procedural Characteristics and Outcomes by Presence of Preoperative Pulmonary Hypertension

	Preoperative mPAP ≤20 mm Hg, N=75	Preoperative mPAP >20 mm Hg, N=413	*P* Value*
Mitral valve replacement vs repair	16.0%	33.2%	0.003
Tricuspid valve repair	8.0%	17.2%	0.06
Cross-clamp time, min	125.9 (44.0)	133.0 (54.4)	0.29
Postoperative ventilation time, h†	3.5 (0–7.1)	5.7 (3.0–17.9)	0.0002
Postoperative ICU time, h†	30.5 (24.0–49.0)	56.0 (29.0–108.5)	<0.0001
Postoperative atrial fibrillation	34.7%	32.4%	0.86
Postoperative myocardial infarction	0%	0.2%	1.0
Postoperative stroke	0%	1.9%	0.46
Postoperative infection, any site	4.0%	6.1%	0.65
Postoperative renal failure	1.3%	7.0%	0.10

Values presented are column percentages for categorical variables or mean (SD) for continuous variables, except where otherwise noted; see below. The postoperative period is defined as the index hospitalization. ICU indicates intensive care unit; and mPAP, mean pulmonary artery pressure.

*Result of *t* test or rank sum test where median and interquartile range are reported.

†Reported as median (interquartile range) because of right skew.

mPAP, PVR, TPG, and right atrial pressure were all associated with decreased 3-year postoperative survival (Figure 3).

A total of 247 patients had a postoperative echocardiogram that estimated pulmonary artery pressure (N=207), had a nondiagnostic echocardiogram

Table 3. Postoperative Echocardiographic Outcomes by Presence of Preoperative Pulmonary Hypertension

	Preoperative mPAP ≤20 mm Hg, N=28	Preoperative mPAP >20 mm Hg, N=203	*P* Value*
Days from surgery to echocardiogram†	95 (59–251)	92 (63–187)	0.74
Ejection fraction, %	53.4 (9.4)	47.8 (14.0)	0.04
Left ventricular end diastolic diameter, cm	4.7 (0.6)	5.1 (0.9)	0.08
Left ventricular end systolic diameter, cm	3.4 (0.6)	3.8 (1.0)	0.047
Pulmonary artery systolic pressure, mm Hg	30.5 (13.3)	36.7 (14.5)	0.053
Residual mitral regurgitation, moderate or greater	7.1%	12.3%	0.55
Postoperative PH			0.036
No PH	57.1%	40.4%	
PH	25.0%	50.2%	
Indeterminate	17.9%	9.4%	
Right ventricular size			0.82
Normal	35.7%	43.8%	
Mildly enlarged	7.1%	8.4%	
Moderately enlarged	0.0%	3.4%	
Severely enlarged	0.0%	0.5%	
Not assessed	57.1%	43.8%	
Right ventricular function			0.49
Normal	50.0%	46.3%	
Mildly reduced	3.6%	7.4%	
Moderately reduced	0.0%	3.0%	
Severely reduced	0.0%	0.0%	
Not assessed	46.4%	43.3%	
Atrial fibrillation	25.0%	32.0%	0.48

Values presented are column percentages for categorical variables or mean (SD) for continuous variables, except where otherwise noted; see below. mPAP indicates mean pulmonary artery pressure; and PH, pulmonary hypertension, defined as mean pulmonary artery pressure >20 mm Hg.

*Result of *t* test or rank sum test where median and interquartile range are reported.

†Reported as median (interquartile range) because of right skew.

(N=24), or died between 42 and 365 days postoperatively (N=16) (Figure 1). Patients with and without an available postoperative echocardiogram were similar with respect to demographics, clinical characteristics, length of follow-up, and first-year mortality (Table S3). These patients were considered available for inclusion in the survival analyses examining post-MVS PH. There was a significant difference in survival between patients who had echocardiographic evidence of postoperative PH and those who did not (P=0.02) (Figure 4A). Grouping patients by PH reversal status, patients who had evidence of persistent PH had higher mortality than those who had no preoperative PH (P=0.03). There was no statistical difference between patients with persistent versus reversed PH (P=0.09) or between patients with reversed PH versus those with no preoperative PH (P=0.09) (Figure 4B). Patients with persistent PH differed from patients with reversed PH with respect to older age (70.0 versus 65.4), but not presurgical patient characteristics including mPAP, cause of MR, choice of valve replacement versus repair, or degree of residual MR (Table S4). Adjusting for timing of the postoperative echocardiogram and the surgeon, postoperative PH was associated with a 102% increase in risk of death (HR, 2.02; 95% CI, 1.17–3.47), or a 20% increase (HR, 1.20; 95% CI, 1.01–1.42) per 10-mm Hg increase in PASP when analyzed continuously. These differences were attenuated and no longer statistically significant after adjustment for all covariates (Table 5).

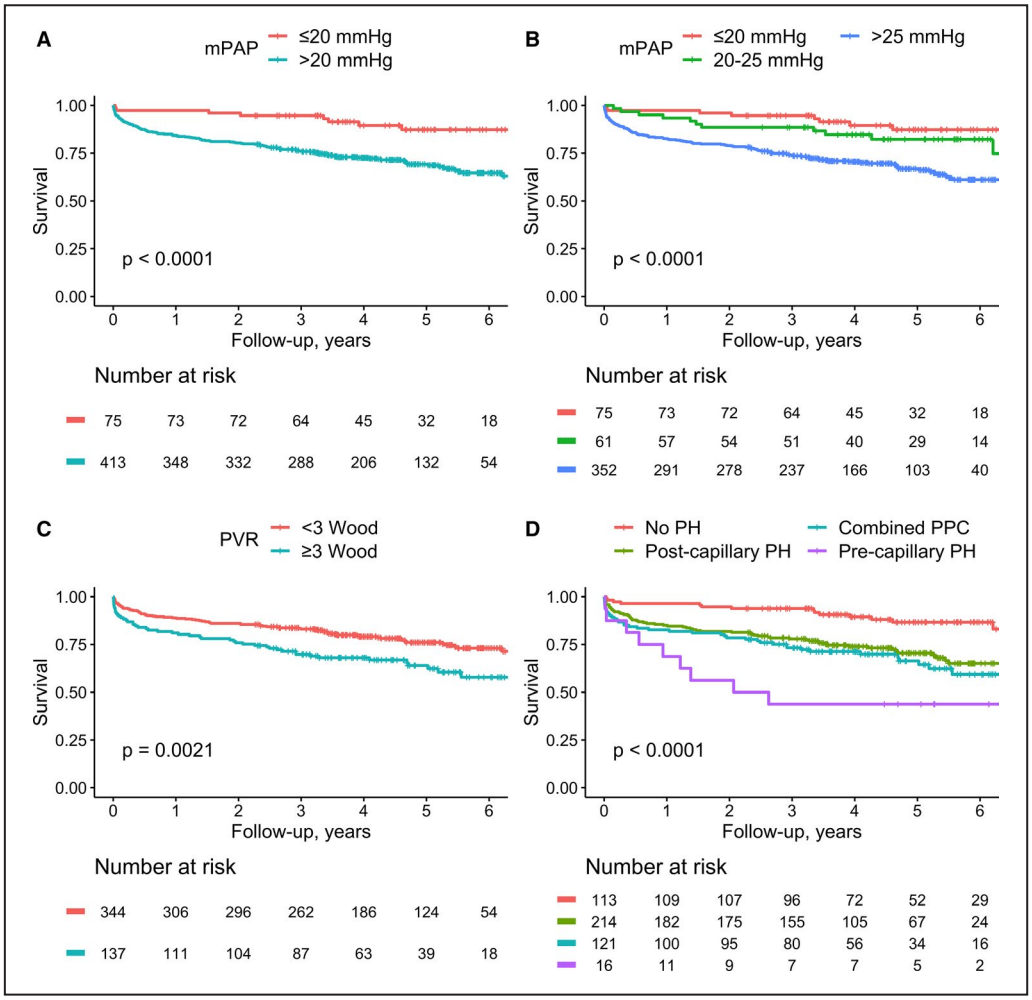


Figure 2. Survival after mitral valve surgery for severe mitral regurgitation by pulmonary hypertension status.
Cumulative survival after mitral valve surgery for severe mitral regurgitation by (**A** and **B**) mean pulmonary artery pressure (mPAP), (**C**) pulmonary vascular resistance (PVR), and (**D**) pulmonary hypertension (PH) phenotype. Phenotypes include no PH, postcapillary PH, precapillary PH, and combined pre- and postcapillary PH (combined PPC). The no-PH category in (**D**) also includes patients with indeterminate/borderline PH (ie, mPAP 20 to 25 mm Hg, PVR <3 Wood units, and pulmonary capillary wedge pressure ≤15).

Table 4. Preoperative Mean Pulmonary Artery Pressure and Risk of Death

Model	Hazard Ratio (95% CI) Continuous per 10-mm Hg mPAP	*P* Value	Hazard Ratio (95% CI) Categorical mPAP >20 mm Hg vs ≤20 mm Hg	*P* Value
Model 1: Timing of catheterization and surgeon	1.51 (1.31, 1.75)	<0.0001	3.38 (1.65, 6.94)	0.0008
Model 2: Model 1+age, sex, body mass index	1.46 (1.25, 1.70)	<0.0001	2.96 (1.43, 6.12)	0.003
Model 3: Model 2+clinical covariates*	1.38 (1.13, 1.68)	0.001	1.79 (0.83, 3.89)	0.14

Hazard ratio for death for each 10-mm Hg increase in mean pulmonary artery pressure (mPAP).

*Clinical covariates: type of mitral valve surgery (repair or replacement), cause of mitral regurgitation (primary vs secondary), concomitant aortic valve surgery, concomitant tricuspid valve surgery, concomitant coronary artery bypass grafting, diabetes mellitus, hypertension, prior clinical heart failure, preoperative ejection fraction, serum creatinine, platelet count, and albumin.

DISCUSSION

In this large, retrospective analysis of patients undergoing MVS for MR, the presence of both preoperative and postoperative PH was associated with an increased risk of death. Our study was novel in the incorporation of multiple preoperative hemodynamic variables for patients undergoing MVS. Invasively measured

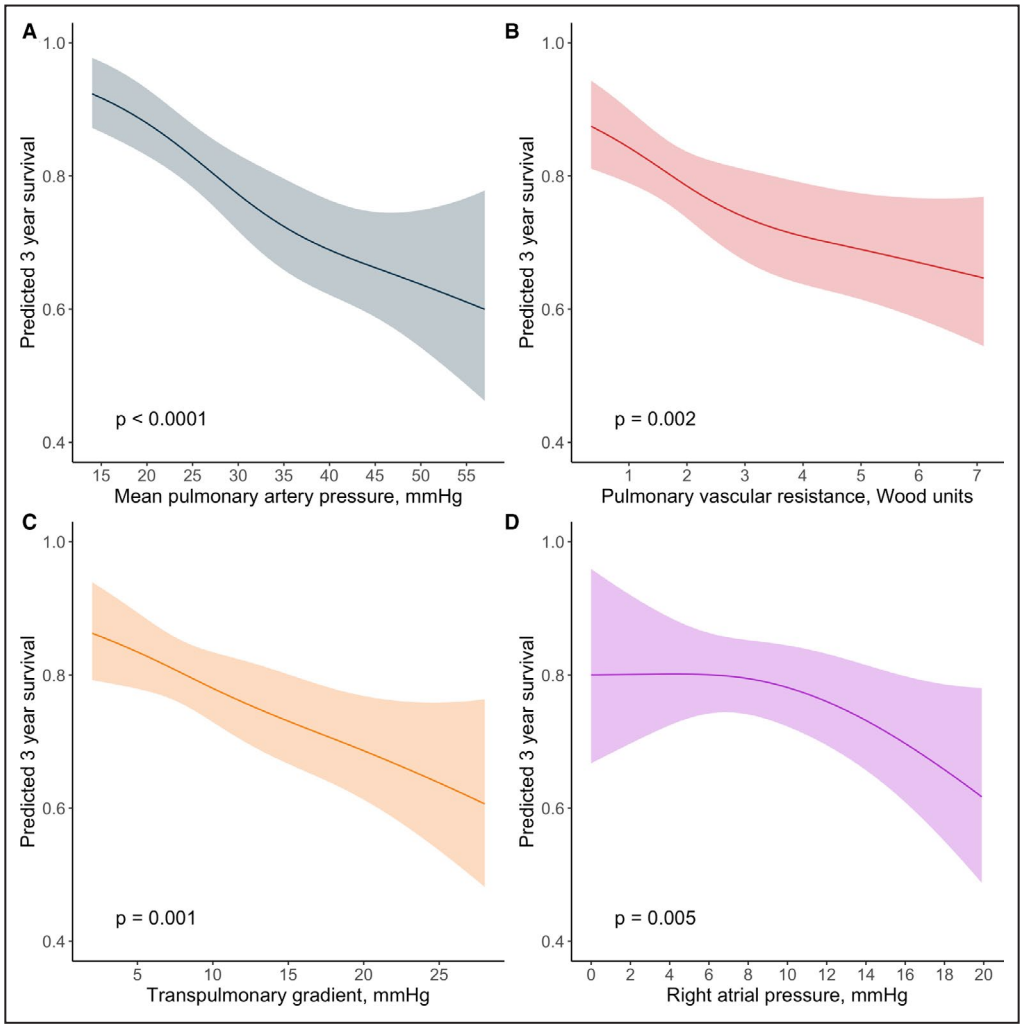


Figure 3. Predicted 3-year survival postoperatively for preoperative hemodynamic parameters. Survival is predicted at 3 years postoperatively for a hypothetical male patient of cohort average age and body mass index for ranges of (**A**) mean pulmonary artery pressure, (**B**) pulmonary vascular resistance, (**C**) transpulmonary gradient, and (**D**) right atrial pressure. **D**, Additionally adjusted for pulmonary capillary wedge pressure and predicted for a wedge of 20 mm Hg. Shaded areas represent 95% confidence intervals.

mPAP was predictive of long-term mortality even after adjustment for patient and procedural characteristics. Additionally, we found that increased preoperative PVR and TPG were also associated with decreased long-term survival. Notably, among the identified subgroups of PH, patients with pure precapillary disease appeared to have the lowest overall survival, although comparisons to other phenotypes were limited by the small number of patients with isolated precapillary disease (N=16). Finally, our study is the first to demonstrate an association between postoperative pulmonary hypertension and survival in a post-MVS cohort.

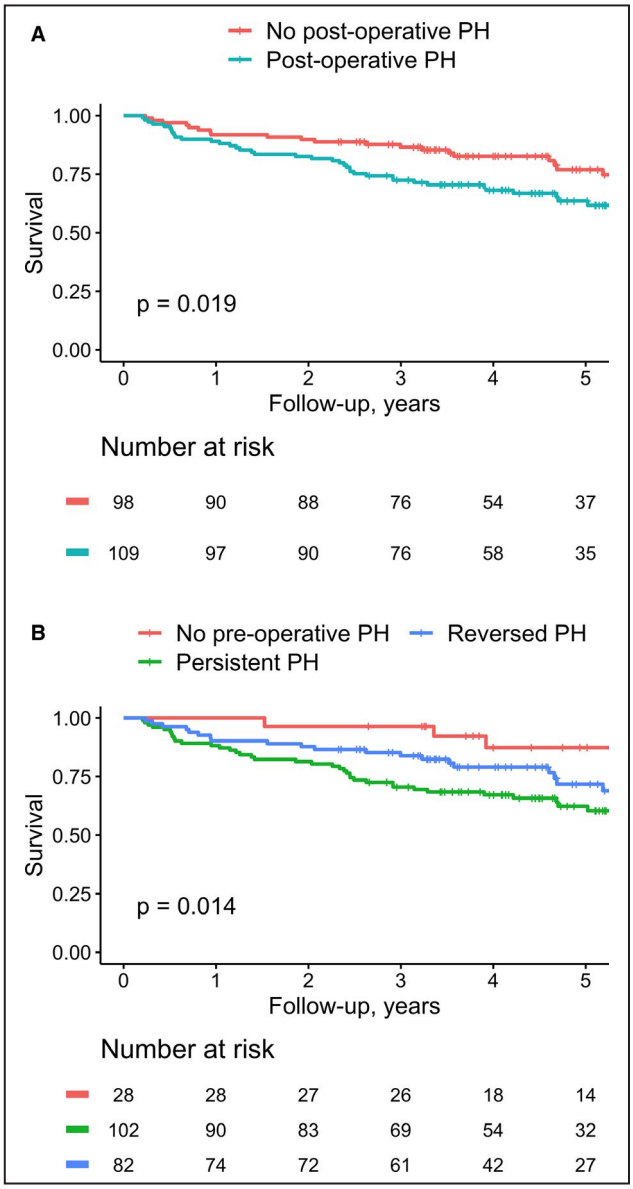


Figure 4. Survival by postoperative pulmonary hypertension (PH).
Overall survival in people with echocardiographic evidence of (**A**) postoperative PH and (**B**) reversibility of preoperative PH. For patients stratified by postoperative PH, stratification can only occur after diagnostic echocardiogram is performed in year 1.

We found PASP ≥35 mm Hg on follow-up echocardiographic examination to be associated with an over 2-fold increase in mortality risk, although the effect was diminished with adjustment.

Two previous investigations have used a registry-based approach to examine the clinical course of patients with severe MR and PH both under medical management and undergoing MVS.[26,27] In both studies, baseline PASP, as measured by Doppler echocardiography, was broadly predictive of mortality. An additional series of 3 investigations[18–20] reported that preoperative systolic pulmonary pressure was predictive of outcomes; however, preoperative timing was variably defined, and only one small (N=46) investigation used primarily invasive measurement of pulmonary artery pressures.[18] We expand upon these findings, showing that PH, as defined by gold-standard invasive measurement[28] was associated with increased postoperative mortality. We note a high prevalence of PH in our study (84%), significantly higher than prior studies. We attribute this to our use of a more liberalized PH definition of mPAP >20 mm Hg as endorsed by recent guidelines and the use of gold-standard invasive PH assessment, which is more highly sensitive than echocardiography.[29] When categorized into 3 subgroups, patients with an mPAP newly reclassified by the PH definition change (mPAP >20 mm Hg and <25 mm Hg) were not statistically distinguishable from patients without PH (mPAP ≤20 mm Hg). This suggests that for PH in the context of severe MR, 25 mm Hg might be a more clinically useful threshold than 20 mm Hg; however, more work should be undertaken to explore this further.

We designed the present study to examine the various components of pulmonary hemodynamics in addition to mPAP. We found that elevated TPG and PVR were both associated with higher mortality after adjustment. This may suggest that the degree of pulmonary vascular remodeling, and not simply retrograde transmission of mitral V waves, is an important predictor of postoperative outcomes. It is hypothesized that development of increased vascular resistance is a downstream response to elevated hydrostatic pressure in the left atrium.[8] Initial compensation for MR is typically left atrial remodeling in the setting of large regurgitant volume followed by left ventricular hypertrophy and dilation in response to an obligate increase in stroke volume. Over time, progressive left ventricular dysfunction, along with a decline in left atrial compliance, result in increased passive filling pressures and pulmonary venous hypertension. Sustained elevation of left atrial pressure can lead to disruption of the alveolar-capillary network and pulmonary vasculature remodeling resulting in a potentially irreversible pulmonary arterial hypertension.[9,10] Among the population of patients with severe MR, it is possible that development of increased

Table 5. Postoperative Estimated Pulmonary Artery Systolic Pressure and Risk of Death

Model	Hazard Ratio (95% CI) Continuous per 10-mm Hg PASP	*P* Value	Hazard Ratio (95% CI) Categorical PASP ≥35 mm Hg vs <35 mm Hg	*P* Value
Model 1: Timing of echocardiography and surgeon	1.20 (1.01, 1.42)	0.03	2.02 (1.17, 3.47)	0.01
Model 2: Model 1+age, sex, body mass index	1.14 (0.96, 1.37)	0.13	1.77 (1.02, 3.07)	0.04
Model 3: Model 2+clinical covariates*	1.10 (0.91, 1.35)	0.33	1.55 (0.85, 2.85)	0.15

Hazard ratio for death for each 10-mm Hg increase in estimated pulmonary artery systolic pressure (PASP).

*Clinical covariates: type of mitral valve surgery (repair or replacement), cause of mitral regurgitation (primary vs secondary), concomitant aortic valve surgery, concomitant tricuspid valve surgery, concomitant coronary artery bypass grafting, diabetes mellitus, hypertension, prior clinical heart failure, preoperative ejection fraction, serum creatinine, platelet count, and albumin.

PVR and TPG are related to length of exposure to the deleterious effects of severe MR and would be an avenue for further study.

Preoperative right ventricular dysfunction, typically assessed via echocardiography, is associated with poor cardiac surgical outcomes.[30–32] Here, we show that right atrial pressure (ie, right ventricular filling pressure) was a predictor of longitudinal mortality independent of PCWP (left ventricular filling pressure). This may imply that the proportionality of right ventricular functional impairment to left ventricular impairment may have additive prognostic value. Interestingly, examination of a spline-modeled prediction plot showed a potential threshold effect at a right atrial pressure of ≈8 mm Hg (Figure 3D). Whether this is a clinically meaningful and useful threshold may benefit from additional study. An important caveat is that we lacked universal echocardiographic right ventricular assessment; thus, our analysis is necessarily limited to hemodynamics and does not include right ventricular structure or imaging-based function.

There may be an important role of tricuspid regurgitation in postoperative hemodynamics and outcomes. In our study, about twice as many patients with preoperative PH had significant tricuspid regurgitation compared with patients without PH; accordingly, concomitant tricuspid valve surgery was performed more frequently in those with PH. Furthermore, patients with persistent postoperative PH frequently had moderate or more severe tricuspid regurgitation on postoperative echocardiogram (Table S4). Our analysis focused on the role of PH on postoperative mortality and treated concomitant tricuspid surgery as a confounder; thus, the study was not designed to comment on the role of concomitant tricuspid repair or replacement, especially on a much longer time scale than what we studied. This would be a fertile area for future investigation, especially on the role of adjuvant percutaneous tricuspid valve procedures as the technology develops further in that field.

Our finding of increased mortality among patients with postoperative PH is consistent with similar investigations in cohorts undergoing interventions for aortic stenosis and mitral stenosis. In patients with severe aortic stenosis undergoing transcutaneous aortic valve intervention, persistent PH was associated with increased long-term mortality.[15,33,34] Estimates varied depending on PH definition and covariate adjustment. For example, persistent severe PH (right ventricular systolic pressure >60) was shown to be associated with a higher 2-year crude overall mortality (50% versus 19%).[33] In another study, postoperative PH was associated with an 82% increase in risk of all-cause mortality after adjustment.[15] Similar findings were seen in patients with persistent PH after surgical aortic valve replacement.[16] In patients undergoing MVS for severe mitral stenosis, risk factors for persistent PH after surgery have been examined, but the association between postoperative PH and mortality has not been well studied.[35,36]

We found a higher risk of long-term mortality among patients after MVS with evidence of postsurgical PH. The magnitude of association was large: an almost 2-fold increase in risk of death among patients with evidence of postoperative PH compared with those without. We note that the effect size was slightly attenuated after adjustment and no longer met statistical significance in some models. However, our postadjustment estimates could not exclude a clinically relevant association between postoperative PH and mortality. A larger sample size is likely required to definitively answer this question, and we believe this should encourage a large, multi-institutional effort to study the relation between pulmonary hemodynamics and outcomes in patients undergoing valvular interventions. Although our study is observational, our finding of a clinically meaningful increase in postoperative mortality in patients with PH undergoing MVS raises the important question of whether patients would benefit from earlier MVS to avoid PH, often thought of as a late complication of longstanding disease. We believe this should be considered, and our study should motivate further prospective inquiry.

We note several strengths to our investigation. We used a gold-standard invasive study to characterize preoperative hemodynamics of a large group of

patients undergoing MVS for severe MR. Our sample size allowed for adjustment of a large number of covariates to examine the independent association between exposures of interest with mortality. Although not available in all patients, we were able to assess for postoperative PH using echocardiography in a large number of patients during follow-up. Finally, physician reviewers adjudicated indications for MVS in all cases to ensure a homogeneous cohort of patients undergoing MVS for a primary or coprimary indication of severe MR.

Limitations

We note that this is an observational study; the timing of surgery and optimization of preoperative hemodynamics was determined by treating physicians and surgeons. Given the uncommon use of invasive hemodynamic study after MVS, postoperative echocardiography was most commonly used to screen for PH. Nonetheless, such noninvasive study can be viable means of identifying severity of PH, although it is limited with regard to differentiating subgroups of PH.[37,38] Echocardiograms were not read by a single core laboratory and may have been subject to different local practices, especially with respect to assessment of central venous pressure to estimate PASP using the tricuspid regurgitant jet velocity. However, all echocardiogram reports included in the analysis were overread by one or more authors. We also acknowledge that while our choices of echocardiographic definitions of PH are supported by expert consensus recommendations,[24] the diagnostic accuracy of echocardiography in the assessment of PH has not been consistently revisited since the 2018 update of the definition of PH to the new, lower mPAP threshold of >20 mm Hg.[39] In our study, we repeated models using both continuous and categorical approaches and found the analyses broadly consistent with one another, lessening the emphasis on specific cutoff values. We also allowed for a wide window in which patients may have post-MVS echocardiographic examinations to capture a large number of patients for study. Such a design leaves our analysis susceptible to immortal time bias. However, we note that time to echocardiogram was similar between patients with and without postoperative PH. Other parameters, such as heart failure hospitalizations, quality of life, and functional assessment, were not available but could be equally valuable. Finally, we note that our study is not intended to study the question of specific treatment for MR-associated PH. Although there is literature to suggest the possibility of treatment with pulmonary vasodilators,[40,41] particularly for patients with elevated PVR,[42] the design of this study was not intended to comment on this question. No patient in our cohort was discharged from their index hospitalization on direct pulmonary vasodilator therapy.

CONCLUSIONS

PH is an adverse consequence of chronic, severe MR. Elevated mPAP and PVR ≥3 Wood units at baseline were associated with increased mortality after MVS. Additionally, postoperative PH continues to be associated with an increased risk of death. Future studies evaluating clinical and echocardiographic risk factors for the development of PH in MR may help optimize surgical timing and improve clinically meaningful outcomes.

ARTICLE INFORMATION

Received July 7, 2020; accepted January 4, 2021.

Affiliations

From the Center for Pulmonary Vascular Biology and Medicine, Pittsburgh Heart, Lung, Blood, and Vascular Medicine Institute, Pittsburgh, PA (M.V.G., A.H., S.Y.C.); Division of Cardiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA (M.V.G.); Division of Cardiology (D.S., G.V., A.C., K.S., R.A.N., F.T., S.R.M., S.Y.C.) and Department of Medicine (M.L.), University of Pittsburgh School of Medicine, Pittsburgh, PA; and Cardiovascular Imaging Center, Minneapolis Heart Institute, Abbott Northwestern Hospital, Minneapolis, MN (J.L.C.).

Acknowledgments

The authors wish to thank Rachel P. Ogilvie, PhD, MPH, for her review of the study design. We acknowledge the Clinical and Translational Science Institute for mortality data via National Institutes of Health grant UL1 TR001857.

Sources of Funding

This work was supported by the National Institutes of Health (R01 HL124021, HL 122596, HL 138437, and UH2/UH3 TR002073); American Heart Association (18EIA33900027) (Dr Chan) and a University of Pittsburgh Medical Center Heart and Vascular Institute Fellow Research Grant (Dr Shpilsky).

Disclosures

Dr Chan has served as a consultant for Aerpio, Zogenix, and United Therapeutics; is a director, officer, and shareholder in Numa Therapeutics; and has held research grants from Actelion and Pfizer. Dr Chan has filed patent applications on the targeting of metabolism in pulmonary hypertension. The remaining authors have no disclosures to report.

Supplementary Material

Data S1
Tables S1–S4
Figures S1–S2

REFERENCES

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet*. 2006;368:1005–1011. DOI: 10.1016/S0140-6736(06)69208-8.
2. Suri RM, Vanoverschelde J-L, Grigioni F, Schaff HV, Tribouilloy C, Avierinos J-F, Barbieri A, Pasquet A, Huebner M, Rusinaru D, et al. Association between early surgical intervention vs watchful waiting and outcomes for mitral regurgitation due to flail mitral valve leaflets. *JAMA*. 2013;310:609–616. DOI: 10.1001/jama.2013.8643.

3. Ling LH, Enriquez-Sarano M, Seward JB, Tajik AJ, Schaff HV, Bailey KR, Frye RL. Clinical outcome of mitral regurgitation due to flail leaflet. *N Engl J Med*. 1996;335:1417–1423. DOI: 10.1056/NEJM199611073351902.
4. Sandoval Y, Sorajja P, Harris KM. Contemporary management of ischemic mitral regurgitation: a review. *Am J Med*. 2018;131:887–895. DOI: 10.1016/j.amjmed.2018.01.048.
5. D'Agostino RS, Jacobs JP, Badhwar V, Fernandez FG, Paone G, Wormuth DW, Shahian DM. The Society of Thoracic Surgeons adult cardiac surgery database: 2018 update on outcomes and quality. *Ann Thorac Surg*. 2018;105:15–23. DOI: 10.1016/j.athoracsur.2017.10.035.
6. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Fleisher LA, Jneid H, Mack MJ, McLeod CJ, O'Gara PT, et al. 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*. 2017;135:e1159–e1195. Available at https://www.ahajournals.org/doi/10.1161/CIR.0000000000000503. Accessed February 12, 2020.
7. Lancellotti P, Martinez C, Bernard A. Pulmonary pressures and outcome in primary mitral regurgitation: paradigm shift from rung to ladder. *J Am Coll Cardiol*. 2016;67:2962–2964. DOI: 10.1016/j.jacc.2016.04.025.
8. Vachiéry J-L, Adir Y, Barberà JA, Champion H, Coghlan JG, Cottin V, De Marco T, Galiè N, Ghio S, Gibbs JSR, et al. Pulmonary hypertension due to left heart diseases. *J Am Coll Cardiol*. 2013;62:D100–D108. DOI: 10.1016/j.jacc.2013.10.033.
9. Magne J, Pibarot P, Sengupta PP, Donal E, Rosenhek R, Lancellotti P. Pulmonary hypertension in valvular disease: a comprehensive review on pathophysiology to therapy from the HAVEC Group. *JACC Cardiovasc Imaging*. 2015;8:83–99. DOI: 10.1016/j.jcmg.2014.12.003.
10. Patel H, Desai M, Tuzcu EM, Griffin B, Kapadia S. Pulmonary hypertension in mitral regurgitation. *J Am Heart Assoc*. 2014;3:e000748. DOI: 10.1161/JAHA.113.000748.
11. Yang B, DeBenedictus C, Watt T, Farley S, Salita A, Hornsby W, Wu X, Herbert M, Likosky DS, Bolling SF. The impact of concomitant pulmonary hypertension on early and late outcomes following surgery for mitral stenosis. *J Thorac Cardiovasc Surg*. 2016;152:394–400.e1. DOI: 10.1016/j.jtcvs.2016.02.038.
12. Fawzy ME, Osman A, Nambiar V, Nowayhed O, El DA, Badr A, Canver CC. Immediate and long-term results of mitral balloon valvuloplasty in patients with severe pulmonary hypertension. *J Heart Valve Dis*. 2008;17:485–491.
13. Maoqin S, Guoxiang H, Zhiyuan S, Luxiang C, Houyuan H, Liangyi S, Ling Z, Guoqiang Z. The clinical and hemodynamic results of mitral balloon valvuloplasty for patients with mitral stenosis complicated by severe pulmonary hypertension. *Eur J Intern Med*. 2005;16:413–418. DOI: 10.1016/j.ejim.2005.02.012.
14. Luçon A, Oger E, Bedossa M, Boulmier D, Verhoye JP, Eltchaninoff H, Iung B, Leguerrier A, Laskar M, Leprince P, et al. Prognostic implications of pulmonary hypertension in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation: study from the FRANCE 2 Registry. *Circ Cardiovasc Interv*. 2014;7:240–247. DOI: 10.1161/CIRCINTERVENTIONS.113.000482.
15. Masri A, Abdelkarim I, Sharbaugh MS, Althouse AD, Xu J, Han W, Chan SY, Katz WE, Crock FW, Harinstein ME, et al. Outcomes of persistent pulmonary hypertension following transcatheter aortic valve replacement. *Heart*. 2018;104:821–827. DOI: 10.1136/heartjnl-2017-311978.
16. Melby SJ, Moon MR, Lindman BR, Bailey MS, Hill LL, Damiano RJ. Impact of pulmonary hypertension on outcomes after aortic valve replacement for aortic valve stenosis. *J Thorac Cardiovasc Surg*. 2011;141:1424–1430. DOI: 10.1016/j.jtcvs.2011.02.028.
17. Zlotnick DM, Ouellette ML, Malenka DJ, DeSimone JP, Leavitt BJ, Helm RE, Olmstead EM, Costa SP, DiScipio AW, Likosky DS, et al. Effect of preoperative pulmonary hypertension on outcomes in patients with severe aortic stenosis following surgical aortic valve replacement. *Am J Cardiol*. 2013;112:1635–1640. DOI: 10.1016/j.amjcard.2013.07.025.
18. Kainuma S, Taniguchi K, Toda K, Funatsu T, Kondoh H, Nishino M, Daimon T, Sawa Y. Pulmonary hypertension predicts adverse cardiac events after restrictive mitral annuloplasty for severe functional mitral regurgitation. *J Thorac Cardiovasc Surg*. 2011;142:783–792. DOI: 10.1016/j.jtcvs.2010.11.031.
19. Le Tourneau T, Richardson M, Juthier F, Modine T, Fayad G, Polge A-S, Ennezat P-V, Bauters C, Vincentelli A, Deklunder G. Echocardiography predictors and prognostic value of pulmonary artery systolic pressure in chronic organic mitral regurgitation. *Heart*. 2010;96:1311–1317. DOI: 10.1136/hrt.2009.186486.
20. Ghoreishi M, Evans CF, DeFilippi CR, Hobbs G, Young CA, Griffith BP, Gammie JS. Pulmonary hypertension adversely affects short- and long-term survival after mitral valve operation for mitral regurgitation: implications for timing of surgery. *J Thorac Cardiovasc Surg*. 2011;142:1439–1452. DOI: 10.1016/j.jtcvs.2011.08.030.
21. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2019;53:1801913. DOI: 10.1183/13993003.01913-2018.
22. Doherty JU, Kort S, Mehran R, Schoenhagen P, Soman P. ACC/AATS/AHA/ASE/ASNC/HRS/SCAI/SCCT/SCMR/STS 2017 appropriate use criteria for multimodality imaging in valvular heart disease: a report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2017;70:1647–1672. DOI: 10.1016/j.jacc.2017.07.732.
23. Butchart EG, Gohlke-Bärwolf C, Antunes MJ, Tornos P, De Caterina R, Cormier B, Prendergast B, Iung B, Bjornstad H, Leport C, et al. Recommendations for the management of patients after heart valve surgery. *Eur Heart J*. 2005;26:2463–2471. DOI: 10.1093/eurheartj/ehi426.
24. Bossone E, D'Andrea A, D'Alto M, Citro R, Argiento P, Ferrara F, Cittadini A, Rubenfire M, Naeije R. Echocardiography in pulmonary arterial hypertension: from diagnosis to prognosis. *J Am Soc Echocardiogr*. 2013;26:1–14. DOI: 10.1016/j.echo.2012.10.009.
25. Kassambara A, Kosinski M. survminer: drawing survival curves using ggplot2. R package v0.4.4. 2019. Available at: https://CRAN.R-project.org/package=survminer. Accessed January 18, 2021.
26. Mentias A, Patel K, Patel H, Gillinov AM, Sabik JF, Mihaljevic T, Suri RM, Rodriguez LL, Svensson LG, Griffin BP, et al. Effect of pulmonary vascular pressures on long-term outcome in patients with primary mitral regurgitation. *J Am Coll Cardiol*. 2016;67:2952–2961. DOI: 10.1016/j.jacc.2016.03.589.
27. Barbieri A, Bursi F, Grigioni F, Tribouilloy C, Avierinos JF, Michelena HI, Rusinaru D, Szymansky C, Russo A, Suri R, et al. Prognostic and therapeutic implications of pulmonary hypertension complicating degenerative mitral regurgitation due to flail leaflet: a multicenter long-term international study. *Eur Heart J*. 2011;32:751–759. DOI: 10.1093/eurheartj/ehq294.
28. Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016;37:67–119. DOI: 10.1093/eurheartj/ehv317.
29. Abdelkarim I, Althouse AD, Thoma FW, Lee JS, Schindler JT, Gleason TG, Cavalcante JL. The importance of invasive hemodynamics for pulmonary hypertension screening in TAVR patients. *J Am Coll Cardiol*. 2017;70:510–511. DOI: 10.1016/j.jacc.2017.04.061.
30. Peyrou J, Chauvel C, Pathak A, Simon M, Dehant P, Abergel E. Preoperative right ventricular dysfunction is a strong predictor of 3 years survival after cardiac surgery. *Clin Res Cardiol*. 2017;106:734–742. DOI: 10.1007/s00392-017-1117-y.
31. Haddad F, Denault AY, Couture P, Cartier R, Pellerin M, Levesque S, Lambert J, Tardif J-C. Right ventricular myocardial performance index predicts perioperative mortality or circulatory failure in high-risk valvular surgery. *J Am Soc Echocardiogr*. 2007;20:1065–1072. DOI: 10.1016/j.echo.2007.02.017.
32. Ting P-C, Wu VC-C, Liao C-C, Chou A-H, Tsai F-C, Lin P-J, Chen C-Y, Chen S-W. Preoperative right ventricular dysfunction indicates high vasoactive support needed after cardiac surgery. *J Cardiothorac Vasc Anesth*. 2019;33:686–693. DOI: 10.1053/j.jvca.2018.07.048.
33. Sinning J-M, Hammerstingl C, Chin D, Ghanem A, Schueler R, Sedaghat A, Bence J, Spyt T, Werner N, Kovac J, et al. Decrease of pulmonary hypertension impacts on prognosis after transcatheter aortic

valve replacement. *EuroIntervention*. 2014;9:1042–1049. DOI: 10.4244/EIJV9I9A177.
34. Testa L, Latib A, De Marco F, De Carlo M, Fiorina C, Montone R, Agnifili M, Barbanti M, Petronio AS, Biondi Zoccai G, et al. Persistence of severe pulmonary hypertension after transcatheter aortic valve replacement: incidence and prognostic impact. *Circ Cardiovasc Interv*. 2016;9:e003563. DOI: 10.1161/CIRCINTERVENTIONS.115.003563.
35. Briongos Figuero S, Moya Mur JL, García-Lledó A, Centella T, Salido L, Aceña Navarro Á, García Martín A, García-Andrade I, Oliva E, Zamorano JL. Predictors of persistent pulmonary hypertension after mitral valve replacement. *Heart Vessels*. 2016;31:1091–1099. DOI: 10.1007/s00380-015-0700-2.
36. Walls MC, Cimino N, Bolling SF, Bach DS. Persistent pulmonary hypertension after mitral valve surgery: does surgical procedure affect outcome? *J Heart Valve Dis*. 2008;17:1–9; discussion 9.
37. Fisher MR, Forfia PR, Chamera E, Housten-Harris T, Champion HC, Girgis RE, Corretti MC, Hassoun PM. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. *Am J Respir Crit Care Med*. 2009;179:615–621. DOI: 10.1164/rccm.200811-1691OC.
38. D'Alto M, Romeo E, Argiento P, Di Salvo G, Badagliacca R, Cirillo AP, Kaemmerer H, Bossone E, Naeije R. Pulmonary arterial hypertension: the key role of echocardiography. *Echocardiography*. 2015;32(suppl 1):S23–S37. DOI: 10.1111/echo.12283.
39. Ni J-R, Yan P-J, Liu S-D, Hu Y, Yang K-H, Song B, Lei J-Q. Diagnostic accuracy of transthoracic echocardiography for pulmonary hypertension: a systematic review and meta-analysis. *BMJ Open*. 2019;9:e033084. DOI: 10.1136/bmjopen-2019-033084.
40. Villanueva DLE, Agustin RD, Llanes EJ. Pre-operative sildenafil for patients with pulmonary hypertension undergoing mitral valve surgery: a systematic review and meta-analysis. *Cardiol Res*. 2019;10:369–377. DOI: 10.14740/cr962.
41. Rex S, Schaelte G, Metzelder S, Flier S, de Waal EEC, Autschbach R, Rossaint R, Buhre W. Inhaled iloprost to control pulmonary artery hypertension in patients undergoing mitral valve surgery: a prospective, randomized-controlled trial. *Acta Anaesthesiol Scand*. 2008;52:65–72. DOI: 10.1111/j.1399-6576.2007.01476.x.
42. Davila CD, Forfia PR. Management of severe pulmonary hypertension in patients undergoing mitral valve surgery. *Curr Treat Options Cardiovasc Med*. 2015;17:382. DOI: 10.1007/s11936-015-0382-1.

SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

In creating multivariable Cox models in the primary analysis, we conducted a complete-case analysis only. However, several patients were missing one more of the covariates included. We therefore conducted a missing case analysis, comparing patients with one more missing covariates with those who are considered complete cases.

To explore the characteristics of patients who reversed pre-operative pulmonary hypertension (PH) and those who did not, we compared two groups with respect to baseline, operative, and other characteristics. The two groups were described using mean (SD) and compared t-test for continuous variables or χ^2 test for categorical variables.

We additionally explored whether one of several complications in the immediate post-operative period (atrial fibrillation, myocardial infarction, stroke, infection, or renal failure) impacted overall survival. The immediate post-operative period is defined as the duration of the index hospitalization during which mitral valve surgery (MVS) occurred. Cohorts of patients with and without a significant complication were visualized with the Kaplan-Meier method and compared using a log-rank test.

Several exploratory analyses were performed examining the relation between other patient characteristics and survival. In the first analysis, we examined post-operative survival in patients stratified by both pre-operative PH status and type of MVS (repair, replacement). We then examined longitudinal mortality after stratification by post-operative PH status (reversed vs persistent PH) and type of MVS. Finally, we examined whether presence of atrial fibrillation on post-operative echocardiogram was associated with mortality by use of a minimally adjusted Cox model which included timing of echocardiogram and surgeon as covariates.

Supplemental Results

Table S1 shows results of the complete case analysis. The two groups were largely comparable. Serum creatinine represented the most commonly missing covariate.

Compared to patients who had reversal of pre-operative PH, patients who did not have reversal of PH had increased prevalence of mildly enlarged and dysfunctional right ventricles (**Table S4**). However, we note that post-operative assessment and high frequency of missing data limits interpretation of this finding. and those who did not. Patients with persistent and reversed PH were otherwise similar with respect to demographics, surgical characteristics, and degree of residual mitral regurgitation.

Detailed index hospital records were not available for 5 patients. Among the 483 patients with detailed hospital records, 202 (41%) had an immediate post-operative complication, and 281 (58%) did not. Patients without complications had lower overall mortality during longitudinal follow-up (p=0.04, **Figure S1**).

In exploratory analyses, we found that type of MVS (repair or replacement) had little relation to post-operative longitudinal outcomes (**Figure S2**). Patients without pre-operative PH who underwent valve repair had lower overall mortality than patients with PH who underwent either repair or replacement (p=0.003 for both), however other pairwise comparisons were not significant. Specifically, there was no difference in overall survival between patients without PH who underwent repair vs replacement (p=0.45), nor was there a difference between patients with PH who underwent repair vs replacement (p=0.70). When stratified both by MVS type and persistence of PH post-operatively, no differences were seen in overall survival, although the sample size may not be sufficient for such comparisons.

In an exploratory analysis of survival by atrial fibrillation status on post-operative echocardiogram, we did not find a significant relation between presence of atrial fibrillation and mortality in a basic model adjusting for timing of echocardiogram and surgeon (HR = 1.47, 95% CI 0.84-2.59, p=0.17).

Table S1. **Missing covariate analysis.**

	Missing N	Cases missing ≥1 covariate (N=100)	Complete cases (N=388)	P-value
Age, years	0	68.1 (11.7)	66.9 (11.1)	0.36
Female	0	45.0%	44.8%	1.0
Body mass index, kg/m,^{2}	0	27.1 (5.2)	28.3 (5.8)	0.074
Mitral valve replacement	0	31.0%	30.7%	1.0
Combined aortic valve surgery	0	30.0%	28.6%	0.81
Combined tricuspid valve surgery	0	15.0%	19.3%	0.39
Combined CABG	0	44.0%	43.5%	1.0
Diabetes	0	24.0%	30.2%	0.27
Hypertension	0	69.0%	80.9%	0.014
Prior heart failure	0	43.0%	54.9%	0.043
Pre-op ejection fraction, %	0	49.2 (13.5)	49.0 (14.3)	0.90
Serum creatinine, μmol/L	94	76.0 (21.3)	92.1 (62.9)	0.54
Platelets, 10^9 L^{-1}	1	200.0 (60.1)	195.2 (±72.4)	0.54
Serum albumin, g/L	14	34.5 (±4.9)	36.5 (±5.5)	0.003

Values presented are column percentages for categorical variables or mean (SD) for continuous variables.

CABG=coronary artery bypass grafting

Table S2. Causes of death during follow-up.

	Pre-operative mPAP ≤20 mmHg (N=75)	**Pre-operative mPAP >20 mmHg (N=413)**	**Total (N=488)**
Total deaths during follow-up	**8 (10.7%)**	**126 (30.5%)**	**134 (27.5%)**
Follow-up time, years (SD)	4.6 (1.6)	3.8 (2.0)	3.9 (2.0)
Cardiovascular deaths	0 (0%)	39 (31%)	39 (29%)
Heart failure	0 (0%)	17 (13%)	17 (13%)
Sudden cardiac death	0 (0%)	13 (10%)	13 (10%)
Myocardial infarction	0 (0%)	2 (2%)	2 (1%)
Cerebrovascular event	0 (0%)	4 (3%)	4 (3%)
Other cardiovascular death	0 (0%)	3 (2%)	3 (2%)
Cancer	1 (13%)	4 (3%)	5 (4%)
Infectious causes	1 (13%)	19 (15%)	20 (15%)
Other causes	0 (0%)	9 (7%)	9 (7%)
Unknown causes	6 (75%)	54 (43%)	60 (45%)

Values shown are N (%) of all deaths in the column group, except for the first row, where percentage of all patients in column is shown.

Table S3. **Comparison of patients with and without post-operative echocardiograms.**

	No echocardiogram (N=227)	**Echocardiogram (N=231)**	**P-value**
Age, years	67.1 (10.9)	67.1 (11.4)	0.95
Female	101 (44.5%)	108 (46.8%)	0.64
Body mass index, kg/m,^{2}	27.7 (5.1)	28.4 (6.2)	0.20
Valve replacement (vs. repair)	66 (29.1%)	72 (31.2%)	0.68
Combined aortic valve surgery	164 (72.2%)	166 (71.9%)	1.0
Combined tricuspid valve surgery	195 (85.9%)	179 (77.5%)	0.022
Combined coronary artery bypass	148 (65.2%)	162 (70.1%)	0.27
Diabetes	60 (26.4%)	69 (29.9%)	0.47
Hypertension	173 (76.2%)	188 (81.4%)	0.21
Prior heart failure	111 (48.9%)	122 (52.8%)	0.45
Pre-op ejection fraction, %	51.1 (13.1)	47.8 (14.6)	0.01
Follow-up time, years	4.3 (1.8)	4.0 (1.8)	0.17
Died during follow-up	39 (17.2%)	65 (28.1%)	0.005
Died during first year	16 (7.0%)	21 (9.1%)	0.49

Values presented are column percentages for categorical variables or mean (SD) for continuous variables. Comparison of characteristics between patients with and without post-operative echocardiograms. Patients who died prior to the echocardiogram eligibility window (days 42-

365) are excluded from the table. Included in the "with echocardiogram" column are 24 patients who had an echocardiogram but did not have quantification of pulmonary hypertension.

Table S4. Characteristics of patients with persistent vs reversed pulmonary hypertension.

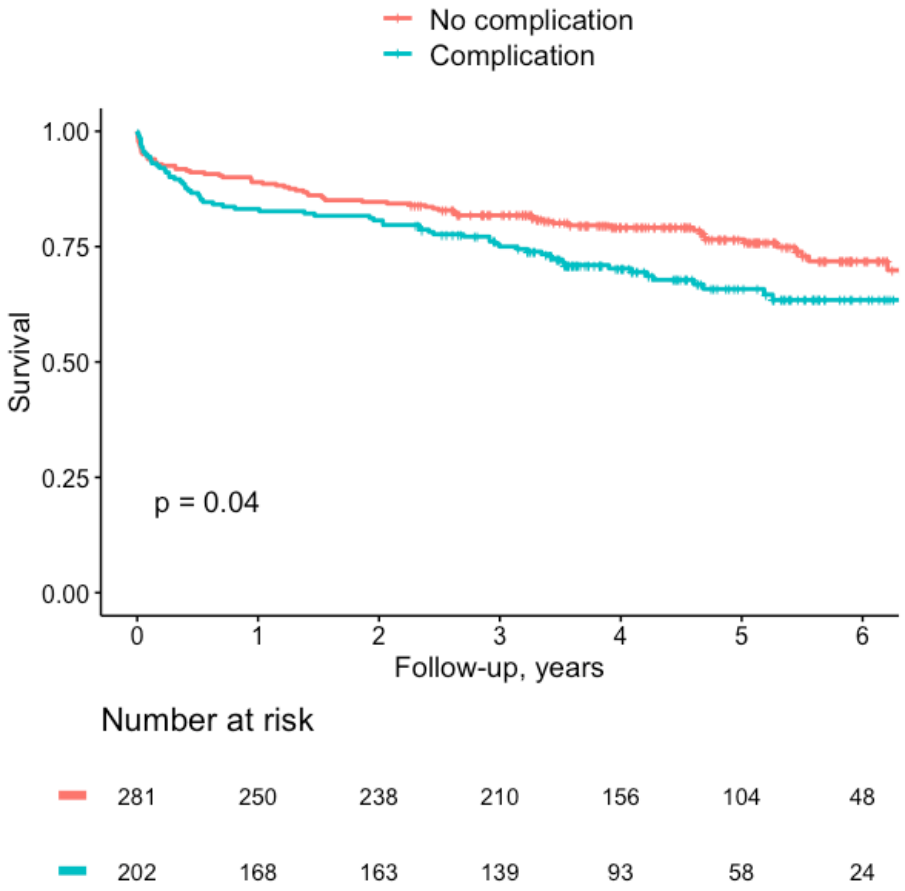
	Persistent PH (N=102)	Reversed PH (N=82)	P-value
Age, years	70.0 (10.3)	65.4 (13.1)	0.009
Female	52.0%	41.5%	0.18
Body mass index, kg/m,^{2}	28.6 (6.4)	28.9 (6.4)	0.77
Pre-operative ejection fraction, %	46.4 (14.4)	47.3 (16.0)	0.68
Diabetes	41 (40.2%)	22 (26.8%)	0.063
Hypertension	91 (89.2%)	67 (81.7%)	0.20
Dyslipidemia	73 (71.6%)	55 (67.1%)	0.52
Dialysis	4 (3.9%)	4 (4.9%)	1.0
Current smoking	18 (17.6%)	18 (22.0%)	0.58
Hematocrit, %	35.6 (4.9)	37.0 (5.3)	0.079
Platelets, 10^9 L^{-1}	199.5 (80.0)	195.1 (69.6)	0.70
Serum creatinine, µmol/L	92.4 (74.6)	100.1 (78.6)	0.53
Serum albumin, g/L	35.6 (5.4)	35.6 (5.3)	0.98
Mitral valve replacement	34.3%	25.6%	0.26
Primary mitral regurgitation	50 (49.0%)	42 (51.2%)	0.88
Days from catherization to surgery, medial (IQR)	9 (3, 38)	10 (4, 27)	0.58
Right atrial pressure, mmHg	9.8 (5.5)	9.7 (4.8)	0.99
Mean pulmonary artery pressure, mmHg	34.4 (9.0)	34.3 (9.5)	0.93
Pulmonary capillary wedge pressure, mmHg	21.5 (6.8)	22.3 (7.6)	0.47
Transpulmonary gradient, mmHg	12.7 (6.5)	12.0 (7.4)	0.49

Pulmonary vascular resistance, Wood units	2.9 (1.9)	2.6 (2.0)	0.34
Cardiac output, L/min	4.8 (1.2)	5.1 (1.7)	0.25
Cardiac index, L/min/m^2	2.5 (0.7)	2.5 (0.7)	0.90
Days from surgery to echocardiogram, median (IQR)	101 (69, 205)	86 (56, 176)	0.13
Post-operative ejection fraction, %	46.4 (15.0)	48.1 (13.3)	0.42
Post-operative LV end diastolic diameter, cm	5.0 (0.9)	5.1 (0.8)	0.57
Post-operative LV end systolic diameter, cm	3.8 (1.1)	3.8 (1.0)	0.73
Residual mitral regurgitation (≥moderate)	16 (15.7%)	7 (8.5%)	0.18
Tricuspid regurgitation (≥moderate)	41 (40.2%)	11 (13.4%)	<0.0001
Post-operative right ventricular size			0.043
Normal	43 (42.2%)	39 (47.6%)	
Mildly enlarged	15 (14.7%)	2 (2.4%)	
Moderately enlarged	4 (3.9%)	3 (3.7%)	
Severely enlarged	1 (1.0%)	0 (0.0%)	
Not assessed	39 (38.2%)	38 (46.3%)	
Post-operative right ventricular function			0.026
Normal	44 (43.1%)	44 (53.7%)	
Mildly reduced	13 (12.7%)	2 (2.4%)	
Moderately reduced	4 (3.9%)	2 (2.4%)	
Severely reduced	0.0%	0.0%	
Not assessed	41 (40.2%)	34 (41.5%)	

Values presented are column percentages for categorical variables or mean (SD) for continuous variables, except where otherwise noted. All patients described had pre-operative pulmonary

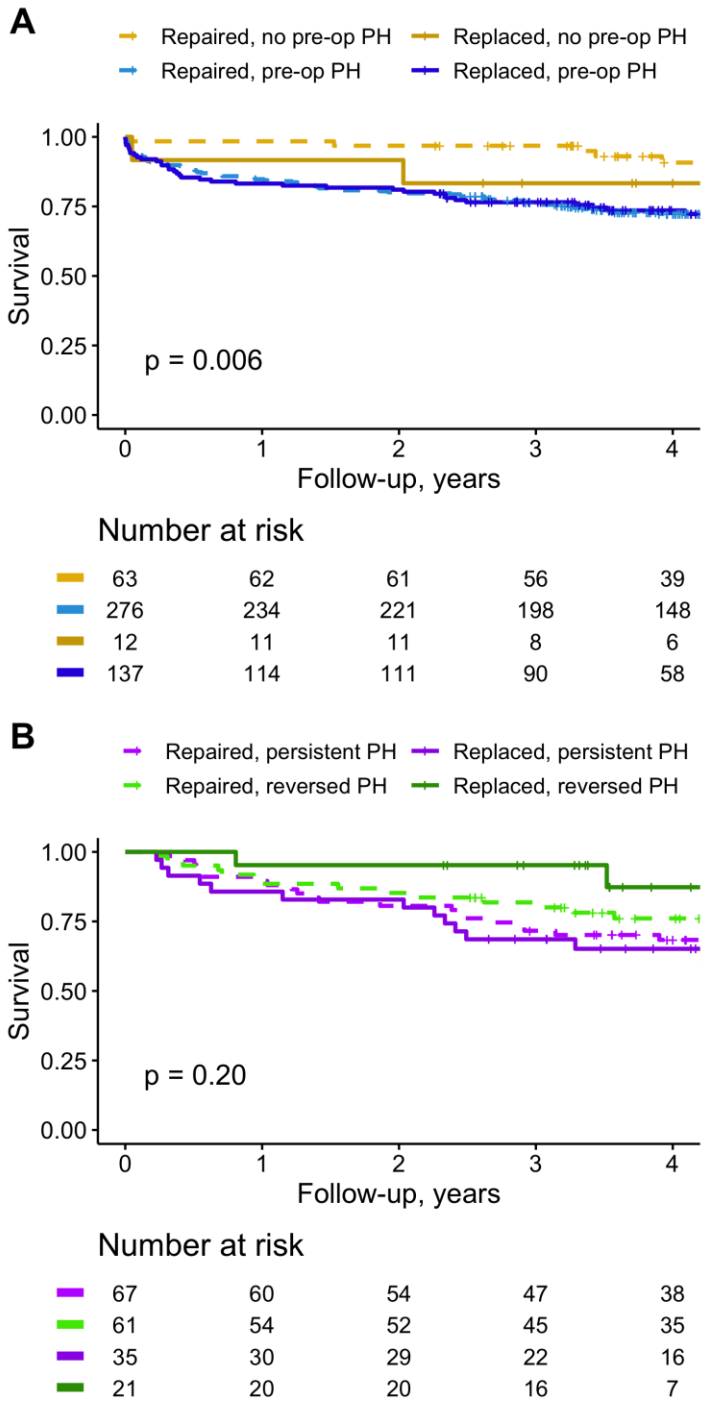
hypertension by right heart catheterization. P-values are t-test or chi-squared test except when variable is described as medical (IQR); in such cases rank sum test is used. LV=left ventricular; PH=pulmonary hypertension.

Figure S1. Post-operative survival according to presence of post-operative complication.



A post-operative complication is defined as atrial fibrillation, myocardial infarction, stroke, infection, or renal failure occurring during index hospitalization after mitral valve surgery.

Figure S2. Longitudinal outcomes after mitral valve repair or replacement in patients with pulmonary hypertension.



Longitudinal survival after mitral valve surgery by type of procedure (valve repair or replacement) and pulmonary hypertension (PH). Patients are additionally stratified by (A)

presence of pre-operative PH, or (B) persistence of pre-operative PH after surgery. P-value is for overall heterogeneity.