CLINICAL RESEARCH STUDY

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Clinical Predictors of Mortality in Patients with Moderate to Severe Mitral Regurgitation

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ABSTRACT

BACKGROUND: Mitral regurgitation is the most common form of valvular heart disease worldwide, however, there is an incomplete understanding of predictors of mortality in this population. This study sought to identify risk factors of mortality in a real-world population with mitral regurgitation.

METHODS: All patients with moderate or severe mitral regurgitation were identified at a single center from January 1, 2016 to August 31, 2017. Multivariate regression was performed to evaluate variables independently associated with all-cause mortality.

RESULTS: A total of 490 patients with moderate (76.3%) or severe (23.7%) mitral regurgitation due to primary (20.8%) or secondary (79.2%) etiology were identified. The mean age was 66.7 years; 50% were male. At a median follow-up of 3.1 years, the incidence of all-cause mortality was 30.1%, heart failure hospitalization 23.1%, and mitral valve intervention 11.6%. Of 117 variables, multivariate analysis demonstrated 5 that were independently predictive of mortality: baseline creatinine (hazard ratio [HR] 1.2; 95% CI, 1.0-1.3; $P = .02$), right atrial pressure by echocardiogram (HR 1.3; 95% CI, 1.07-1.55; $P = .008$), hemoglobin (HR 0.65; 95% CI, 0.52-0.83; $P = .001$), hospitalization for heart failure (HR 1.6; 95% CI, 1.1-2.4; $P = .015$), and mitral valve intervention (HR 0.40; 95% CI, 0.16-0.83; $P = .049$).

CONCLUSION: In this retrospective, pragmatic analysis of patients with moderate or severe mitral regurgitation, admission for heart failure exacerbation, elevated right atrial pressure, renal dysfunction, anemia, and lack of mitral valve intervention were independently associated with increased risk of all-cause mortality. Whether these risk factors may better identify select patients who may benefit from more intensive monitoring or earlier intervention should be considered in future studies.

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KEYWORDS: Mitral valve; Mitral valve insufficiency; Mortality

INTRODUCTION

Mitral regurgitation is the most common form of valvular heart disease worldwide and continues to increase in prevalence in North America, coinciding with an aging population.[1-3] This vast burden of mitral regurgitation is an important contributor to health care expenditures, in its symptomatic form contributing an additional $7.6 billion in annual spending in the United States, the costliest of any valvular disease.[4] In both primary form due to intrinsic valvular disease and secondary form due to left ventricular dysfunction, mitral regurgitation tends to be progressive in nature and leads to further detrimental cardiac remodeling. The presence of mitral regurgitation, regardless of the etiology, is associated with significant negative impact on quality of life, morbidity, and all-cause mortality.[5]

A complete understanding of the prognosis and clinical predictors of medically managed or corrected mitral regurgitation has proven arduous. Previously, the availability of effective surgical therapies drove the majority of efforts

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toward understanding the long-term prognosis and factors that predict outcomes of primary mitral regurgitation. In the recent era, with more effective interventional therapies becoming available for secondary mitral regurgitation, punctuated by the publication of the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial, understanding the prognosis and factors affecting these outcomes may help us better identify patient populations that can potentially be targeted for these therapies.[6] With this hypothesis, we sought to determine long-term outcomes as well as predictors of outcomes in a contemporary, real-world population with moderate or severe mitral regurgitation.[7]

CLINICAL SIGNIFICANCE

- Mitral regurgitation remains the most common valvular heart disease worldwide; morbidity and mortality remain high.
- Baseline creatinine, right atrial pressure, hemoglobin, hospitalization for heart failure, and lack of mitral intervention were associated with mortality.
- Mitral regurgitation severity, and quantitative variables by which mitral regurgitation is graded, were not predictive of mortality.
- Application of these findings may better inform prognosis, management, and timing of intervention in patients with mitral regurgitation.

METHODS

Study Population and Design

Consecutive patients >18 years old who underwent transthoracic echocardiogram at Oregon Health & Science University, a quaternary care academic medical center, between January 1, 2016 and August 31, 2017 were sequentially screened using Cardiac Intelligence (Mpirik, Milwaukee, Wis) software to identify subjects with moderate or severe mitral regurgitation, without restriction on etiology. Considering the high frequency of observing mild mitral regurgitation and relatively low event rate in this population, we included only moderate and severe mitral regurgitation in order to have a sufficiently high cardiovascular event rate to detect meaningful associations among predictors and outcomes. Mpirik Cardiac Intelligence searches the electronic health record to identify echocardiographic evidence of mitral regurgitation and other valvular heart disorders. Initial identification of patients with mitral regurgitation was assessed by quantitate (proximal isovelocity surface area radius, effective regurgitant orifice area, regurgitant volume and fraction) and qualitative (report summary and conclusions) data. The severity of mitral regurgitation was assessed as trace, mild, moderate, or severe by echocardiography according to current American Society of Echocardiography guidelines, which remained consistent for the duration of the study period.[8] Thus, all echocardiographic measurements and classifications remained standardized and centralized during the study period. All studies and variables extracted by Cardiac Intelligence software were reviewed by authors OK, KM, KS, and SF to verify accuracy. Subjects were excluded if they had prior complex congenital heart disease or incomplete clinical follow-up.

Following index echocardiogram, patients were managed as part of standard clinical care without a prescribed protocol for therapy. Electronic medical records were reviewed and demographics, comorbid conditions, laboratory data, and therapies were extracted at the time of index transthoracic echocardiogram. Clinical outcomes including all-cause mortality, heart failure-related hospitalization, and need for mitral valve intervention (surgical mitral valve intervention, percutaneous mitral valve intervention, transplant, or left-ventricular assist device) were independently extracted and adjudicated by the authors (OK, KM, KS, SF) from the electronic medical record, as well as clinical interviews with treating physicians, patients, and (when necessary) next of kin. Patients were followed until death or August 31, 2019.

A total of 117 potential predictive variables were extracted, consisting of 52 demographic and clinical variables and 65 hemodynamic and anatomic variables obtained from the echocardiograms. All variables were obtained closest to the index date (ie, the date of the diagnosis of moderate or severe mitral regurgitation by echocardiogram during the study period).

This study was approved by the institutional review board of Oregon Health & Science University; requirement for written informed consent was waived given its retrospective nature.

Statistical Analysis

Patient characteristics are reported as frequencies and percentages for categorical variables and mean with standard deviations for continuous variables. Differences in baseline demographic, clinical, and morphologic variables were tested with unpaired Student's t test for continuous variables and chi-squared test for categorical variables.

A single-variable proportional hazard model was used to determine the relationship each of the 117 extracted variables had with all-cause mortality. Each variable was used individually in a proportional hazards model, and those demonstrating significance were subsequently included in multivariate modeling. For multivariate analysis, we compared all variables against each other for collinearity and accounted for this prior to our analysis utilizing principal component analysis as the first component. We heuristically included only variables that had at least 400 observations. In total, 90 variables met the above criteria and were included in our subsequent variable selection analysis (Supplementary Table 1, available online). Continuous variables were analyzed as such, with the exception of left

ventricular ejection fraction, which was semi-continuous, using a threshold of >60% on the basis of current guidelines.[9] Model performance was assessed using the widely applicable information criterion and the receiver operator curve's area under the curve criteria.[10] To calculate the widely applicable information criteria, the log-likelihood of the data conditioned upon the posterior distributions of the parameters was evaluated. The receiver operator curve's area under the curve was calculated by evaluating the mean survival probability, conditioned on parameter posterior distributions, for each patient over the minimum observation time, which was approximately 3 years. A series of head-to-head comparisons were performed to settle upon a final model.

All probability values were 2-tailed, and P values < .05 were considered significant.

RESULTS

Demographics and Clinical Characteristics

A total of 490 patients, comprised of 374 (76.3%) with moderate mitral regurgitation and 116 (23.7%) with severe mitral regurgitation, were included for analysis (Table 1). Mitral regurgitation was more frequently secondary (79.2%), compared with primary (20.8%), in etiology (Table 1). At diagnosis, the mean age was 66.7 ± 15.9 years; 245 (50.0%) were female, and there was a high prevalence of comorbid conditions: hypertension 63%; atrial fibrillation or flutter 46.7%; coronary artery disease 39.2%; and chronic kidney disease 32.9% (Table 1). The majority of patients (57.6%) demonstrated a history of clinical heart failure. Medical therapy included use of beta-blockers (60.8%), angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (45.5%), aldosterone antagonist (11.4%), and loop diuretic (51.6%) (Table 1). Baseline mitral regurgitation parameters on echocardiogram included mean regurgitant volume of 42.2 ± 27.0 mL and effective regurgitant orifice area of 0.29 ± 0.25 cm^2. The mean ejection fraction was mildly reduced (45.3 ± 17.4%), however, 109 (22.2%) patients had an ejection fraction >60%.

Classification of patients by severity of mitral regurgitation is presented in Supplementary Table 2 (available online). Patients with severe mitral regurgitation had lower mean systolic blood pressure and lower incidence of chronic kidney disease and hypertension. Subjects with severe mitral regurgitation demonstrated greater mean regurgitant volume and effective regurgitant orifice area, and more advanced cardiac remodeling with greater mean left ventricular diastolic diameter, left atrial diameter, and pulmonary artery systolic pressures (Supplementary Table 2) than subjects with moderate mitral regurgitation.

Table 1 Baseline Characteristics of the Patients

	Total Cohort (N = 490)
Demographics	
Age, years	66.7 ± 15.9
Male, n (%)	245 (50.0%)
Systolic blood pressure, mm Hg	124.9 ± 23.1
Diastolic blood pressure, mm Hg	69.5 ± 15.1
Mitral regurgitation: etiology	
Secondary, n (%)	388 (79.2%)
Primary, n (%)	102 (20.8%)
Prolapse	41 (8.7%)
Rheumatic	13 (2.7%)
Degenerative	12 (2.5%)
Other	36 (7.3%)
Comorbid conditions	
Atrial fibrillation/flutter, n (%)	229 (46.7%)
Coronary artery disease, n (%)	192 (39.2%)
History of CABG, n (%)	62 (12.6%)
History of PCI, n (%)	56 (11.4%)
Diabetes mellitus, n (%)	139 (28.4%)
Chronic kidney disease, n (%)	161 (32.9%)
Dialysis-dependent, n (%)	22 (4.5%)
Hypertension, n (%)	309 (63.0%)
Heart failure, n (%)	282 (57.6%)
Peripheral artery disease, n (%)	60 (12.2%)
Former or current smoker, n (%)	239 (48.8%)
Solid tumor, and grade, n (%)	104 (21.2%)
History of stroke or TIA, n (%)	100 (20.4%)
Index echocardiogram data	
Ejection fraction, %	45.3 ± 17.4
LVIDd, cm	5.31 ± 1.11
LVIDs, cm	4.12 ± 1.40
Left atrial volume (a-l biplane), mL	103.6 ± 73.6
Right atrial pressure, mm Hg	8.69 ± 4.91
Aortic stenosis, more than mild, n	21 (4.3%)
RVSP, mean, mm Hg	44.13 ± 15.98
EROA area, cm^2	0.291 ± 0.260
Regurgitant volume, mL	42.2 ± 27.0
Laboratory data	
Nt-ProBNP, pg/mL	12,358 ± 33,282
Hemoglobin, g/dL	11.9 ± 2.7
Medical therapy	
ACE/ARB, n (%)	223 (45.5%)
Beta blocker, n (%)	298 (60.8%)
Calcium channel blocker, n (%)	73 (14.9%)
Loop diuretic, n (%)	253 (51.6%)
ARNI, n (%)	4 (0.8%)
Antiarrhythmic, n (%)	92 (18.8%)
Anticoagulation, n (%)	173 (35.3%)

ACE = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; CABG = coronary artery bypass grafting; EROA = effective regurgitant orifice area; LVIDd = left ventricular internal diameter end-diastole; LVIDs = left ventricular internal diameter end-systole; Nt-ProBNP = N-terminal pro B-type natriuretic peptide; PCI = percutaneous coronary intervention; RVSP = right ventricular systolic pressure; TIA = transient ischemic attack.

Clinical End Points

Patient were followed for a median of 3.1 years (interquartile range 2.48-3.42), during which time 151 patients died, thus, the incidence of all-cause mortality was 30.1% (Figure, Table 2). Mortality at 1 year was 16.7% in the total population, and similar between those with moderate and severe mitral regurgitation (16.7% vs 17.2%, P = .87).

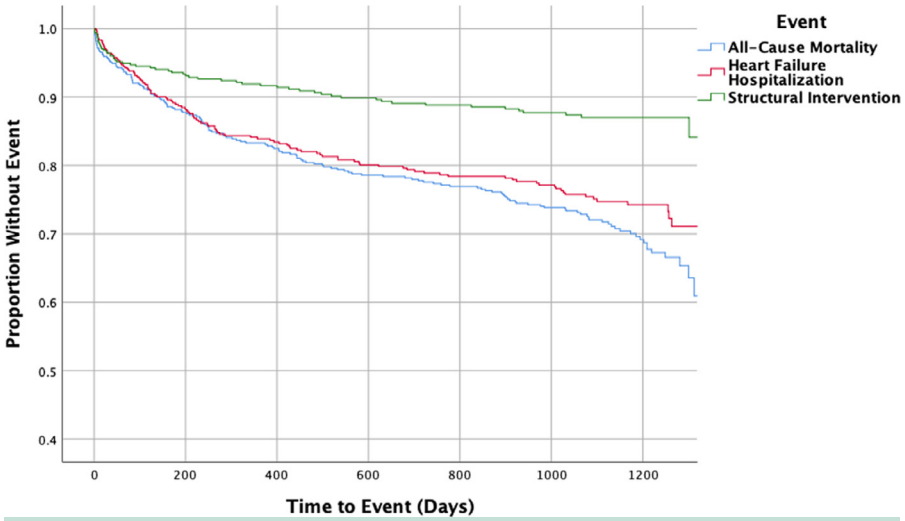

Figure Regression analysis demonstrating time to event in patients with moderate to severe mitral regurgitation.

Patients who died during the study period were older and had more frequent comorbid conditions, but similar frequency of moderate and severe mitral regurgitation at index echocardiogram compared with those who survived (Supplementary Table 3, available online). While regurgitant volume and effective regurgitant orifice area were similar between groups, patients who died had lower mean ejection fraction, greater mean left atrial volume, greater rates of heart failure hospitalization during the study period, and were less likely to receive a mitral valve intervention during the study period (Supplementary Table 3).

Admission for heart failure was common; during follow-up, 113 patients were hospitalized for heart failure with 1-year and 3-year rates of 16.3% and 23.1%, respectively (Figure, Table 2).

A total of 57 (11.6%) subjects underwent mitral valve intervention (Figure). Patients receiving intervention were, on average, younger (61.2 ± 14.5 years vs 67.4 ± 16.0 years, $P = .006$), had generally lower frequency of comorbid conditions (hypertension: 42.1% vs 66.0% $P < .001$, chronic kidney disease: 15.8% vs 35.3% $P = .0035$, atrial fibrillation: 42.1% vs 47.4%, $P = .45$, coronary artery disease: 28.0% vs 40.7% $P = .067$), were more likely to have primary effective regurgitant orifice area (49.1% vs 16.4%, $P < .001$), and more likely to have severe mitral regurgitation (63.2% vs 18.5%, $P < .001$) than subjects who had no intervention.

Predictors of All-Cause Mortality

Multivariable analysis demonstrated 5 variables that were independently predictive of mortality: baseline creatinine (hazard ratio [HR] 1.2; 95% confidence interval [CI], 1.0-1.3; $P = .02$), right atrial pressure by echocardiogram (HR 1.3; 95% CI, 1.07-1.55; $P = .008$), and hemoglobin (HR 0.65; 95% CI, 0.52-0.83; $P = .001$) as continuous variables, as well as hospitalization for heart failure (HR 1.6; 95% CI, 1.1-2.4; $P = .015$) and mitral valve intervention (HR 0.40; 95% CI, 0.16-0.83; $P = .049$) during the study period (Table 3). Notably, left ventricular ejection fraction improved model accuracy, thus, it was retained in the analysis, but was not independently predictive of mortality (odds ratio 0.99; 95% CI, 0.97-1.0; $P = .14$). In addition, inclusion of left atrial volume, right ventricular systolic pressure,

Table 2 Primary and Secondary Clinical Outcomes

	Total Population (N = 490)	Etiology	
Outcome		Primary (n = 102)	Secondary (n = 388)
All-cause mortality, n (%)	151 (30.8%)	18 (17.6%)	133 (34.3%)
Heart failure hospitalization, n (%)	113 (23.0%)	6 (5.9%)	107 (27.6%)
Structural heart intervention, n (%)	57 (11.6%)	27 (26.5%)	30 (7.7%)
Heart transplant, n (%)	5 (1.0%)	0 (0%)	5 (1.3%)
Left ventricular assist device, n (%)	9 (1.8%)	1 (1.0%)	8 (2.0%)
Surgical MV repair or replacement, n (%)	31 (6.3%)	21 (20.5%)	10 (2.6%)
Transcutaneous MV intervention, n (%)	12 (2.4%)	4 (3.9%)	8 (2.1%)

MV = mitral valve.

Table 3 Relation of Major Risk Factors to Observed All-Cause Mortality

Variable	Multivariate Analysis		
	HR	95% CI	*P* Value
Creatinine	1.16	1.02-1.33	.024
Heart failure hospitalization	1.64	1.11-2.42	.015
Hemoglobin	0.65	0.52-0.83	.001
Intervention	0.40	0.16-0.98	.049
Left ventricular ejection fraction	0.99	0.97-1.00	.14
Right atrial pressure	1.29	1.07-1.55	.008

CI = confidence interval; HR = hazard ratio.

effective regurgitant orifice area, and regurgitant volume had no effect on model accuracy, and were not associated with risk of mortality.

DISCUSSION

In this retrospective, real-world analysis of nearly 500 consecutive patients found to have moderate or severe mitral regurgitation on echocardiogram and followed for a median of more than 3 years, we observed a mortality rate of 30.1%, heart failure-related hospitalization rates of 23%, and a mitral valve intervention rate of 11.6%. There were 5 independently predictive variables associated with increased all-cause mortality in this patient population: renal dysfunction, anemia, elevated right atrial pressure estimated by echocardiogram, admission for heart failure, and lack of mitral valve intervention during the study period.

Our study demonstrated an all-cause mortality of 30.1% at 3 years, which is consistent with findings from longitudinal studies of primary mitral regurgitation and lower than that observed with moderate-severe or severe functional mitral regurgitation in the medical management arm of the COAPT trial (46.1% at 2-year follow-up).[6,11] Compared with the COAPT population, which applied a more stringent inclusion criteria, our subjects were younger, had lower frequency of comorbidities, lower proportion of severe mitral regurgitation with inclusion of both primary and secondary etiologies, less left ventricular dilation, and greater mean left ventricular systolic function.[6] Such differences are likely to account, at least in part, for the observed differences in mortality. As the COAPT trial did not evaluate predictors of mortality, and the vast majority of our population did not undergo intervention, our identification of predictors of mortality is important to stratify subjects who are at high risk for mortality with current medical management.

A number of individual diseases as well as the sum of comorbidities have proven to be important prognosticators across many cardiovascular conditions, including mitral regurgitation.[12-14] Of the comorbidities included in our analysis, we found anemia and renal dysfunction to be independently associated with an increased risk of all-cause mortality. Anemia and renal dysfunction have reliably proven to be risk factors for development and adverse outcomes in heart failure, left ventricular hypertrophy, coronary artery disease, and numerous other cardiac conditions.[15] Anemia is common in older adults—the severity of anemia has previously been associated with severity of mitral regurgitation and its presence associated with increased all-cause mortality following repair of severe mitral regurgitation with MitraClip (Abbott, Chicago, Ill).[16-18] Here we demonstrated an association between anemia and long-term mortality in patients with moderate to severe mitral regurgitation. Similarly, renal dysfunction is a known major risk factor for presence and progression of valvular heart disease; in subjects with chronic kidney disease the presence of mitral regurgitation is associated with increased risk of mortality compared with those without.[19] Here we found the complement to be true, demonstrating renal dysfunction to be independently associated with risk of mortality in subjects with moderate to severe mitral regurgitation. Whether the prognostic importance of such factors is a direct cause of worse outcomes or a marker of other causal factors is not clear.

The development of clinical heart failure and progression to hospitalization is an important milestone in the progression of many cardiac conditions and has been identified as a poor prognostic marker.[20,21] We observed that hospitalization for heart failure conferred a significantly increased risk of subsequent mortality during the study period in patients with moderate or severe mitral regurgitation. Moreover, elevated right atrial pressure estimated by echocardiogram at baseline, which may indicate maladaptive hemodynamics or early decompensation, was independently associated with increased mortality. These variables may identify the presence or progression of clinical heart failure and the sequalae thereof, and serve a prognostic importance in this population. Notably, worsening heart failure or admission for heart failure are lacking as a consideration for prognosis or timing of intervention under current guidelines.[8]

We observed an association of mitral valve intervention and decreased risk of all-cause mortality. Although our study was not conducted nor adequate to assess the efficacy of intervention directly, prior randomized controlled trials have demonstrated a marked clinical benefit, including decreased risk of mortality in select populations of both primary and secondary mitral regurgitation.[6,22,23] Despite this, less than half of subjects with guideline-recommended indication for intervention of primary mitral regurgitation, and even fewer with secondary mitral regurgitation, undergo intervention despite the availability of effective therapies.[24] These findings, in context, indicate an unmet need and potential opportunity to mitigate the high mortality seen in this population.

Based on our analysis, we have identified 5 objective and readily available clinical, demographic, and echocardiographic variables, which confer an increased risk of all-cause mortality in moderate or severe mitral regurgitation. An important finding of our study is the lack of mitral regurgitation severity, as well as any quantitative

hemodynamic variable by which grading of mitral regurgitation is recommended under current guidelines, to be independently predictive of mortality. Application of these findings may better inform the prognosis of patients with mitral regurgitation, and in select patient populations may better inform the risk−benefit decision about frequency and type of monitoring and indication and timing of interventions in this population. Whether select patients may benefit from more intensive monitoring, pharmacotherapy, or mitral valve intervention at the onset of identifying elevated filling pressures, volume overload, or hospitalization should be considered in future studies.

Limitations of this study are inherent to its retrospective nature. Given the variability in documentation of symptom burden, this was not adequately captured and analyzed in our data. In addition, there exists real world variation in the optimization of goal-directed medical therapy, which is also consistent in our patient population, which may thus undermine the role of medical therapy and its effects on mortality. The population was underpowered to perform subgroup analysis, and thus, analysis of predictors by specific etiology of mitral regurgitation was not performed. Lastly, this was a single-center study and thus, the findings may not extrapolate to all populations of interest.

CONCLUSIONS

Despite advances in therapy, significant mitral regurgitation continues to be associated with excess mortality, heart failure hospitalizations, and extremely low rate of mitral valve intervention. Consideration should be given to predictors like anemia, renal dysfunction, elevated right atrial pressure, and history of heart failure hospitalization for escalating advanced mitral valve therapy options to potentially improve long-term prognosis in this patient population.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2021.09.004.

Supplementary Table 1 Demographic, Clinical, and Echocardiographic Variables and Relation to Observed All-Cause Mortality, Univariate Analysis

Variable	Univariate Analysis		
	HR	95% CI	*P* Value
ACE/ARB use	0.64	0.46-0.90	.011
Age	1.02	1.00-1.03	.001
AIDS, history of	1.16	0.16-8.3	.882
Aldosterone antagonist use	1.25	0.78-2.0	.362
Anti-arrhythmic medication	1.56	1.07-2.3	.020
Aortic root diameter	0.96	0.92-1.02	.145
Aortic valve area	2.07	1.03-4.15	.055
Aortic valve area - indexed	2.63	0.82-8.55	.121
Aortic valve dimensionless index	0.64	0.26-1.59	.339
Aortic valve mean gradient	0.99	0.97-1.01	.281
Aortic valve peak velocity	0.95	0.76-1.18	.629
Atrial fibrillation, history of	1.21	0.87-1.67	.254
Beta-blocker use	0.81	0.59-1.12	.212
Body surface area	0.78	0.43-1.43	.425
Calcium channel blocker use	0.57	0.33-0.99	.049
Cardiac index	1.01	0.50-2.05	.967
Cardiac output	1.00	0.73-1.38	.977
Chronic kidney disease	2.38	1.73-3.29	< .001
Chronic obstructive pulmonary disease, history of	1.09	0.70-1.69	.694
Connective tissue disease, history of	1.13	0.50-2.56	.766
Coronary artery bypass surgery, history of	1.46	0.95-2.24	.087
Coronary artery disease, history of	1.38	1.00-1.90	.052
Creatinine	1.16	1.07-1.26	.001
Dementia, history of	1.54	0.84-2.85	.171
Diabetes mellitus	1.50	1.07-2.10	.019
Dialysis dependent	3.34	1.96-5.71	< .001
Diastolic blood pressure	0.98	0.97-0.99	.008
Direct anticoagulants use	0.89	0.56-1.41	.624
Effective regurgitant orifice area	0.47	0.14-1.60	.226
Endocarditis, history of	0.21	0.029-1.49	.120
Estimated glomerular filtration rate (EGFR)	0.97	0.978-0.98	< .001
Sex	1.18	0.85-1.63	.320
Heart failure, history of	1.39	0.99-1.95	.059
Heart failure hospitalization	2.17	1.55-3.04	< .001
Heart rate	1.01	1.00-1.02	.021
Hemiplegia, history of	0.53	0.074-3.80	.530
Hemoglobin	0.81	0.75-0.87	< .0001
Hemoglobin A1c	1.01	1.05-1.02	< .0001
Hypertension, history of	1.23	0.87-1.74	.238
Immunocompromised, history of	1.40	0.86-2.26	.174
International normalized ratio	1.17	0.98-1.39	.084
Interstitial lung disease, history of	2.42	1.19-4.94	.016
Intervention	0.22	0.09-0.55	< .001
Isosorbide dinitrate/hydralazine use	2.51	1.32-4.78	.006
Left atrial volume, MOD method	1.01	1.002-1.01	.005
Left atrial volume, a-l biplane	1.00	0.99-1.00	.132
Left ventricular ejection fraction	0.98	0.97-0.99	<.001
Left ventricular outflow tract diameter	0.70	0.38-1.29	.252
Left ventricular outflow tract velocity	0.70	0.35-1.41	.321
Leukemia, history of	1.79	0.66-4.84	.252
Liver disease, history of	1.42	0.79-2.57	.244
Loop diuretic use	1.40	1.01-1.94	.047
LVIDd	1.12	0.97-1.30	.111
LVIDs	1.18	1.05-1.31	.005
Lymphoma, history of	1.78	0.78-4.03	.168
Mean arterial blood pressure	0.99	0.98-1.00	.046
Mean pulmonary artery pressure	1.02	0.99-1.05	.199
Mean right atrial pressure	1.04	0.97-1.12	.289
Mean transmitral gradient	1.02	0.98-1.06	.378
Mediastinal radiation, history of	0.54	0.13-2.20	.393
Mitral regurgitation severity	1.20	0.90-1.60	.200
Mitral valve e/a ratio	1.12	0.92-1.36	.282
Mitral valve inflow, peak e	1.33	0.86-2.06	.206
Mitral valve peak a	1.15	0.69-1.93	.595
Mitral valve TDI E/e'	1.02	1.00-1.05	.016
Myocardial infarction, history of	2.06	1.46-2.89	< .001
Obstructive sleep apnea	1.56	1.06-2.30	.026
Peptic ulcer disease, history of	0.63	0.23-1.70	.364
Percutaneous coronary intervention, history of	1.32	0.84-2.07	.235
Peripheral arterial disease, history of	1.83	1.21-2.78	.005
Platelet count	1.00	0.99-1.00	.835
Pulmonary capillary wedge pressure	1.06	1.02-1.11	.012
Pulmonary vascular resistance	1.01	0.86-1.18	.907
Regurgitant volume	0.99	0.98-1.00	.089
Right atrial pressure	1.10	1.06-1.13	< .001
Right ventricular diastolic pressure	1.00	0.96-1.04	.852
Right ventricular systolic pressure, catheterization	1.01	0.99-1.04	.205
Right ventricular systolic pressure, echocardiogram	1.02	1.01-1.03	< .001
Sacubitril/valsartan use	0.72	0.10-5.15	.745
Solid tumor, history of	1.15	0.78-1.69	.473
Statin use	1.06	0.77-1.47	.714
Stroke or TIA, history of	1.69	1.18-2.4	.005
Systemic vascular resistance	1.00	0.99-1.01	.964
Systolic blood pressure	1.00	0.99-1.01	.561
Tricuspid annular plane systolic excursion	0.51	0.38-0.70	< .001
Thiazide diuretic use	0.60	0.24-1.45	.258
Tobacco use	1.47	1.06-2.03	.023
Tricuspid valve regurgitant velocity	1.59	1.20-2.18	.002
Warfarin use	1.42	0.98-2.10	.069
White blood cell count	1.04	1.01-1.07	.008

ACE = angiotensin converting enzyme inhibitor; AIDS = acquired immunodeficiency syndrome; ARB = angiotensin receptor blocker; CI = confidence interval; HR = hazard ratio; LVIDd = left ventricular internal diameter end-diastole; LVIDs = left ventricular internal diameter end-systole; MOD = biplane method of disk; TIA = transient ischemic attack; TDI = tissue Doppler imaging.

Supplementary Table 2 Baseline Characteristics, By Severity of Mitral Regurgitation

	Moderate MR (n = 374)	Severe MR (n = 116)	*P* Value
Demographics			
Age, years	65.8 ± 15.7	66.3 ± 16.7	.77
Male, n (%)	182 (48.7%)	60 (51.7%)	.56
Systolic blood pressure, mm Hg	126.5 ± 23.3	119.6 ± 21.7	.005
Diastolic blood pressure, mm Hg	70.1 ± 15.2	67.6 ± 14.4	.31
Mitral regurgitation, etiology			
Secondary, n (%)	312 (83.4%)	76 (65.5%)	< .0001
Primary, n (%)	62 (16.6)	40 (34.4%)	< .0001
Prolapse	28 (7.5%)	13 (11.2%)	.21
Rheumatic	9 (2.4%)	4 (3.5%)	.54
Degenerative	8 (2.1%)	4 (3.5%)	.43
Other	17 (4.5%)	19 (15.7%)	< .0001
Comorbid conditions			
Atrial fibrillation/flutter, n (%)	183 (48.9%)	46 (39.7%)	.08
Coronary artery disease, n (%)	145 (38.8%)	47 (40.5%)	.73
History of CABG, n (%)	44 (11.8%)	18 (15.5%)	.29
History of PCI, n (%)	44 (11.8%)	12 (10.3%)	.67
Diabetes mellitus, n (%)	107 (28.6%)	32 (27.6%)	.83
Chronic kidney disease, n (%)	133 (35.6%)	28 (24.1%)	.022
Dialysis dependent, n (%)	19 (5.1%)	3 (2.6%)	.26
Hypertension, n (%)	252 (67.4%)	57 (49.1%)	.0013
Heart failure, n (%)	210 (56.1%)	72 (62.1%)	.26
Peripheral artery disease, n (%)	47 (12.6%)	13 (11.2%)	.70
Former or current smoker, n (%)	193 (51.6%)	46 (39.7%)	.024
Solid tumor, and grade, n (%)	89 (23.8%)	15 (12.9%)	.012
History of stroke or TIA, n (%)	74 (19.8%)	26 (22.4%)	.54
Index echocardiogram data			
Ejection fraction, %	45.7 ± 17.0	44.2 ± 18.8	.42
LVIDd, cm	5.2 ± 1.1	5.6 ± 1.1	.0007
LVIDs, cm	4.1 ± 1.4	4.3 ± 1.5	.19
Left atrial volume (a-l biplane), mL	95.5 ± 43.7	134.7 ± 108.0	.0001
Right atrial pressure, mm Hg	8.4 ± 4.7	9.6 ± 5.3	.02
Aortic stenosis, more than mild, n	16 (4.3%)	5 (4.3%)	.99
RVSP, mean, mm Hg	41.4 ± 13.5	52.2 ± 19.8	.0001
EROA area, cm^2	0.24 ± 0.25	0.41 ± 0.25	.0001
Regurgitant volume, mL	35.9 ± 20.0	59.5 ± 34.5	.0001
Laboratory data			
Nt-ProBNP, pg/mL	13,288 ± 37,000	10,011 ± 20,995	.23
Hemoglobin, g/dL	11.8 ± 2.8	12.0 ± 2.0	.48
Medical therapy			
ACE/ARB, n (%)	168 (44.9%)	55 (47.4%)	.64
Beta-blocker, n (%)	232 (62.0%)	66 (56.9%)	.32
Calcium channel blocker, n (%)	62 (16.6%)	11 (9.5%)	.06
Loop diuretic, n (%)	184 (49.2%)	69 (59.5%)	.053
ARNI, n (%)	3 (0.8%)	3 (2.6%)	.13
Antiarrhythmic, n (%)	68 (18.2%)	24 (20.7%)	.55
Anticoagulation, n (%)	136 (36.4%)	37 (31.9%)	.38

ACE = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; CABG = coronary artery bypass grafting; EROA = effective regurgitant orifice area; LVIDd = left ventricular internal diameter end-diastole; LVIDs = left ventricular internal diameter end-systole; MR = mitral regurgitation; Nt-ProBNP = N-terminal pro B-type natriuretic peptide; PCI = percutaneous coronary intervention; RVSP = right ventricular systolic pressure; TIA = transient ischemic attack.

Supplementary Table 3 Baseline Characteristics, By Outcome

	Deceased (n = 151)	Alive (n = 339)	*P* Value
Demographics			
Age, years	70.3 ± 15.1	65.0 ± 16.1	<.001
Male, n	80 (53.0%)	162 (47.8%)	.29
Systolic blood pressure, mm Hg	124.5 ± 25.9	125.1 ± 21.9	.79
Diastolic blood pressure, mm Hg	67.1 ± 17.3	70.6 ± 13.9	.018
Comorbid conditions			
Atrial fibrillation/flutter, n (%)	76 (50.3%)	153 (45.3%)	.29
Chronic kidney disease, n (%)	95 (62.9%)	86 (25.4%)	<.001
Dialysis-dependent, n (%)	15 (9.9%)	7 (2.1%)	<.001
Coronary artery disease, n (%)	71 (47.0%)	121 (35.7%)	.018
History of CABG, n (%)	23 (15.2)	39 (11.5%)	.25
History of PCI, n (%)	22 (14.6%)	34 (10.0%)	.14
Diabetes mellitus, n (%)	53 (35.1%)	86 (25.4%)	.027
Former or current smoker, n (%)	85 (56.3%)	154 (45.4%)	.026
Heart failure, n (%)	95 (62.9%)	187 (55.2%)	.11
Hypertension, n (%)	102 (67.5%)	207 (61.1%)	.17
Peripheral artery disease, n (%)	27 (17.9%)	33 (9.7%)	.011
Solid tumor, and grade, n (%)	34 (22.5%)	70 (20.6%)	.64
Stroke or TIA, n (%)	42 (27.8%)	58 (17.1%)	.007
Index echocardiogram data			
Moderate MR, n (%)	115 (76.2%)	259 (76.4%)	.95
Severe MR, n (%)	36 (23.8%)	80 (23.6%)	
Ejection fraction, percent	41.1 ± 18.0	47.2 ± 16.9	<.001
LVIDd, cm	5.44 ± 1.23	5.26 ± 1.06	.10
LVIDs, cm	4.39 ± 1.50	4.00 ± 1.34	.004
Left atrium volume (a-l biplane), mL	116.8 ± 68.8	99.2 ± 64.4	.007
Right atrium pressure, mm Hg	10.5 ± 4.91	7.80 ± 4.69	<.001
RVSP, mm Hg	49.0 ± 15.9	41.7 ± 15.5	<.001
EROA area, cm^2	0.29 ± 0.20	0.29 ± 0.36	1.0
Regurgitant volume, mL	38.0 ± 23.8	44.1 ± 28.2	.021
Clinical events			
Heart failure hospitalization, n (%)	55 (36.4%)	58 (17.1%)	<.001
Major intervention, n (%)	5 (3.3%)	52 (15.3%)	<.001
Heart transplant	0 (0%)	5 (1.5%)	.13
Left ventricular assist device	2 (1.3%)	7 (2.1%)	.57
Surgical MV repair or replacement	1 (0.7%)	30 (8.8%)	<.001
Transcutaneous MV intervention	2 (1.3%)	10 (2.9%)	.28
Progression of MR, n (%)	12 (7.9%)	19 (5.6%)	.33
Regression of MR, n (%)	28 (18.5%)	102 (30.1%)	.008
Laboratory data			
Creatinine, mg/dL	1.69 ± 1.5	1.23 ± 1.1	<.001
Hemoglobin, g/dL	11.0 ± 2.2	12.3 ± 2.8	<.001

CABG = coronary artery bypass grafting; EROA = effective regurgitant orifice area; LVIDd = left ventricular internal diameter end-diastole; LVIDs = left ventricular internal diameter end-systole; MR = mitral regurgitation; MV = mitral valve; PCI = percutaneous coronary intervention; RVSP = right ventricular systolic pressure; TIA = transient ischemic attack.