

# Impact of Duration of Mitral Regurgitation on Outcomes in Asymptomatic Patients With Myxomatous Mitral Valve Undergoing Exercise Stress Echocardiography

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**Background**—Significant mitral regurgitation (MR) typically occurs as holosystolic (HS) or mid-late systolic (MLS), with differences in volumetric impact on the left ventricle (LV). We sought to assess outcomes of degenerative MR patients undergoing exercise echocardiography, separated based on MR duration (MLS versus HS).

**Methods and Results**—We included 609 consecutive patients with  $\geq$ III+myxomatous MR undergoing exercise echocardiography: HS (n=487) and MLS (n=122). MLS MR was defined as delayed appearance of MR signal during mid-late systole on continuous-wave Doppler while HS MR occurred throughout systole. Composite events of death and congestive heart failure were recorded. Compared to MLS MR, HS MR patients were older ( $60\pm 14$  versus  $53\pm 14$  years), more were males (72% versus 53%), and had greater prevalence of atrial fibrillation (16% versus 7%; all  $P<0.01$ ). HS MR patients had higher right ventricular systolic pressure (RVSP) at rest ( $33\pm 11$  versus  $27\pm 9$  mm Hg), more flail leaflets (36% versus 6%), and a lower number of metabolic equivalents (METs) achieved ( $9.5\pm 3$  versus  $10.5\pm 3$ ), compared to the MLS MR group (all  $P<0.05$ ). There were 54 events during  $7.1\pm 3$  years of follow-up. On step-wise multivariable analysis, HS versus MLS MR (HR 4.99 [1.21 to 20.14]), higher LV ejection fraction (hazard ratio [HR], 0.94 [0.89 to 0.98]), atrial fibrillation (HR, 2.59 [1.33 to 5.11]), higher RVSP (HR, 1.05 [1.03 to 1.09]), and higher percentage of age- and gender-predicted METs (HR, 0.98 [0.97 to 0.99]) were independently associated with adverse outcomes (all  $P<0.05$ ).

**Conclusion**—In patients with  $\geq$ III+myxomatous MR undergoing exercise echocardiography, holosystolic MR is associated with adverse outcomes, independent of other predictors. (*J Am Heart Assoc.* 2015;4:e001348 doi: 10.1161/JAHA.114.001348)

**Key Words:** mitral regurgitation duration • stress echocardiography and outcomes

Mitral regurgitation (MR) results in volume overload of the left ventricle (LV) and left atrium (LA) with often progressive enlargement and remodeling, a finding associated with worse clinical outcomes.<sup>1,2</sup> Currently, the recommendations for performing mitral valve (MV) surgery are primarily based on instantaneous severity of MR (vena contracta width [VCW] and effective regurgitant orifice area [EROA]), based on previous demonstrations that patients with more-severe quantification of instantaneous MR have worse outcomes.<sup>3–6</sup> However, volumetric impact of MR is determined not only by

its instantaneous severity, but also by its duration in systole.<sup>7</sup> Differences in MR dynamics can affect the degree of volume overload and, potentially, the outcome of these patients. However, in studies evaluating prognosis based on MR severity, little data exist pertaining to outcomes related to systolic duration of MR.<sup>3,8,9</sup>

Duration of MR is typically categorized as holosystolic (HS) or mid-late systolic (MLS). Whereas both forms can result in volume overload and adverse LV remodeling, the changes are less likely to be severe in MLS than HS MR for the same size of regurgitant orifice. A recent study has shown fewer cardiac events in patients with MLS, compared to HS MR.<sup>10</sup> However, this study included patients with lesser severities of MR who were only under medical management, and the differences in outcomes after mitral surgery remain unclear. Variability in duration of myxomatous MR has been recognized clinically and echocardiographically, with HS MR often being thought of as a later or more-severe manifestation of the disease. The specific characteristics of patients with HS versus non-HS MR in patients with myxomatous MV disease being considered for

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surgical intervention have not been previously addressed in a sizeable cohort. Also, optimal timing of MV surgery remains controversial in asymptomatic patients with significant degenerative MR,<sup>11,12</sup> and exercise echocardiography is frequently used in such patients to aid in symptom evaluation, risk stratification, and decision making for appropriate timing of surgery.<sup>13–15</sup> In asymptomatic patients with  $\geq$ III+MR, we sought to (1) characterize the differences between those with HS versus MLS MR and (2) assess whether simultaneous assessment of systolic duration of MR and exercise capacity impacts long-term outcomes in asymptomatic patients with moderate-to-severe (III+) or severe (IV+) myxomatous MR undergoing exercise echocardiography.

## Methods

### Study Design

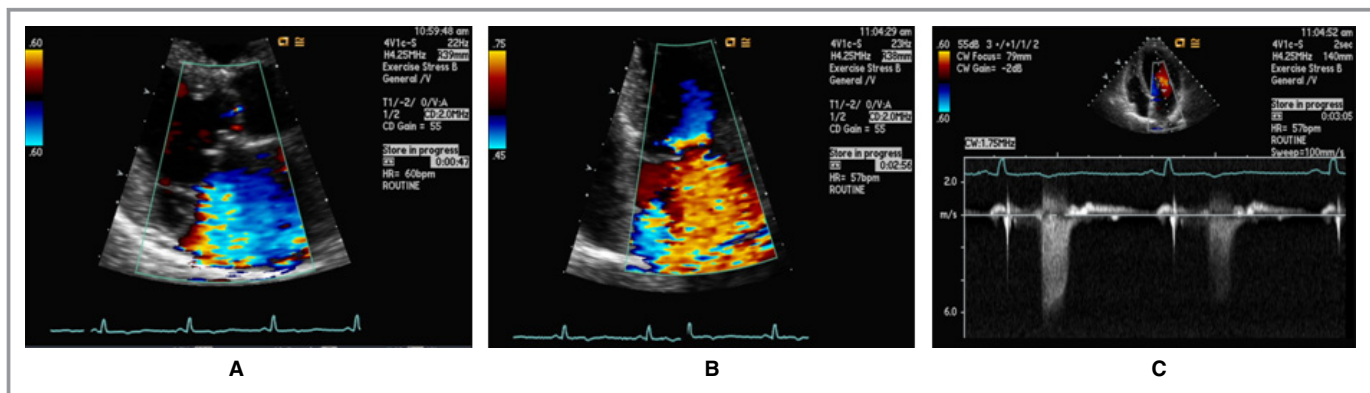
This is an observational retrospective cohort study of 609 consecutive patients with  $\geq$ III+myxomatous MR who underwent treadmill exercise echocardiography at our institution between January 2000 and December 2011 for symptom evaluation and to aid in surgical timing. We excluded patients with functional MR (including ischemic etiology), preceding valvular surgery, hypertrophic cardiomyopathy, rheumatic valvular disease, or greater than mild mitral stenosis. After institutional review board approval, electronic medical records were analyzed for data collection. Baseline clinical and medication history was manually extracted from the electronic health records at a time closest to exercise echocardiography (within 1 month). Presence of paroxysmal (lasting  $\geq$ 30 seconds) or permanent atrial fibrillation (AF) or atrial flutter was recorded. Follow-up clinical data, including time and type of MV surgery, were collected. In those who underwent MV surgery, AF occurring within 30 days postoperatively was not included. Additive Euro score was calculated

in each patient.<sup>16</sup> The decision to perform MV surgery was made by the attending cardiologist and cardiothoracic surgeon, after a thorough clinical and echocardiographic evaluation, based on the recommendations at the time.

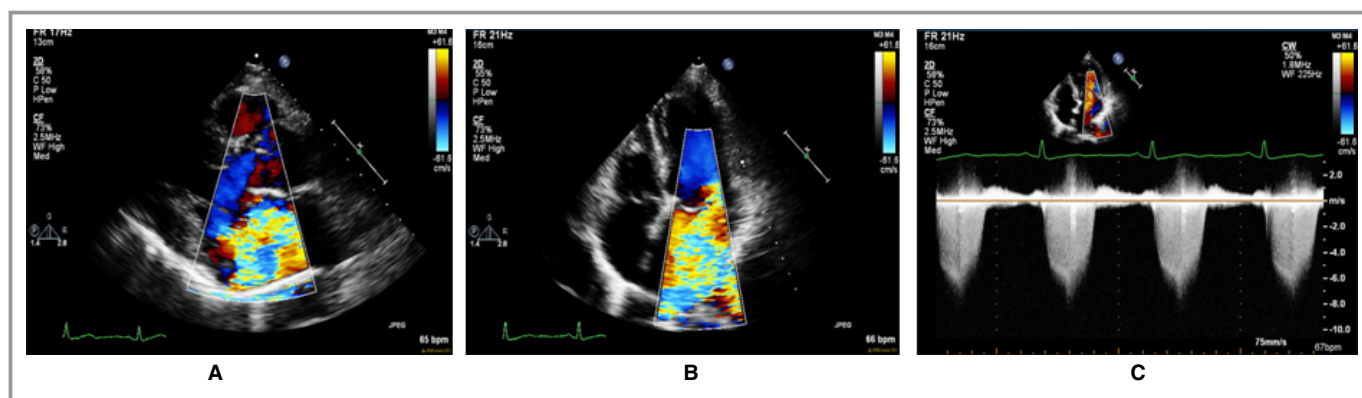
### Resting and Exercise Echocardiography

All patients underwent comprehensive echocardiograms using commercial instruments (Philips Medical Systems, Bothell, WA, Siemens Medical Solution Inc, Malvern, PA, and General Electric, Milwaukee, WA). LV ejection fraction (LVEF), indexed LV dimensions, and left atrial area were measured according to guidelines.<sup>17</sup> At the point of inclusion in this study, all echo images were rereviewed to document the severity of MR, using multiple previously described techniques.<sup>5</sup> Doppler VCW was remeasured in each patient on the parasternal long-axis views in the resting study, and only patients with VCW  $\geq$ 0.5 cm were included.<sup>5</sup> Additionally, we remeasured EROA of the MV and MR regurgitant volume.<sup>5</sup> Also, using continuous-wave Doppler images, we quantified systolic MR duration, relative to valve closing spikes (and/or QRS complex), ranging from a percentage of systole (mid-late) to 100% of systole. MR duration was further confirmed by M-mode through the color Doppler signal. Based on that, patients were subcategorized as MLS-MR (Figure 1) or HS-MR (Figure 2). Because of severity of MR, diastolic function was not reported. Presence of flail mitral leaflet was recorded. Right ventricular (RV) systolic function was measured qualitatively (normal, mild, moderate, or severe). RV systolic pressure (RVSP) was measured at rest.<sup>5</sup>

Subsequently, in conjunction with echocardiography, patients underwent a symptom-limited standard exercise treadmill test using the Bruce protocol. Patients were instructed to hold their medications the day of the test. Blood pressure, heart rate, and electrocardiographic measurements were made at rest, at 1-minute intervals, and for



**Figure 1.** Transthoracic images in a patient with severe late systolic mitral regurgitation. A, Parasternal long-axis color Doppler image, (B) 4-chamber color Doppler image, and (C) spectral Doppler demonstrating late mitral regurgitation.



**Figure 2.** Transthoracic images in a patient with severe holosystolic mitral regurgitation. A, Parasternal long-axis color Doppler image, (B) 4-chamber color Doppler image, and (C) spectral Doppler demonstrating holosystolic mitral regurgitation.

≥6 minutes in recovery. Maximal predicted heart rate (220-age), percent-predicted maximal heart rate, and number of metabolic equivalents (METs) achieved were recorded. We also calculated expected METs, based on age and gender. In men, expected METs were calculated using the Veterans Affairs cohort formula (predicted METs=18-[0.15×age]),<sup>18</sup> whereas in women, the St. James Take Heart Project formula was used (predicted METs=14.7-[0.13×age]).<sup>19</sup> These specific formulae for calculating expected METs have been previously demonstrated in their respective genders to best predict outcomes.<sup>20</sup> We also calculated the following ratio: (METs achieved/age-gender-predicted METs)×100.

Immediately following exercise, peak-stress echocardiographic images were acquired,<sup>21</sup> and the following parameters were assessed: regional wall motion abnormalities for evaluation of ischemia and peak-stress RVSP. We also evaluated changes in LV cavity size (increase, decrease, or no change), suggestive of presence or absence of contractile reserve.<sup>22</sup> Major (sustained ventricular or atrial arrhythmias associated with severe symptoms, hemodynamic compromise, or need for cardioversion) were recorded.

## Follow-up and Outcomes

The date of the patient's first exercise echocardiography at our institution was defined as the beginning of the observational period. Follow-up was ascertained by chart review, and we recorded the date at which events occurred. New-stage C/D congestive heart failure (CHF), observed during follow-up after baseline exercise echocardiogram, was recorded after chart review by a single reviewer, according to guidelines (new-onset dyspnea, effort intolerance, or fatigue).<sup>23</sup> Mortality data were obtained from medical records or from the U.S. Social Security Death Index database (last inquiry in June 2014). A composite outcome of mortality and progression to CHF were defined as the primary endpoint. Patients were

censored at the time of event or last follow-up at our institution. In patients who developed multiple endpoints, the time to the first event was utilized as an event time cutoff. Additionally, stroke was defined as neurologic impairment lasting >24 hours with radiographic evidence of brain ischemia or hemorrhage. In patients who had undergone MV surgery, the date and type of MV surgery was recorded. Time to MV surgery was recorded. However, given that stress echocardiography may have directly impacted the decision to operate, we did not use surgical timing as an endpoint.

## Statistical Analysis

Continuous variables are expressed as mean±SD and/or median and compared using analysis of variance (for normally distributed variables) or Mann-Whitney's test (for non-normally distributed variables). Categorical data are expressed as percentage and compared using the chi-squared test. To assess outcomes, Cox's proportional hazards analysis was performed. We initially tested the association of potential predictors of composite outcomes in a univariable fashion. Subsequently, we performed forward step-wise multivariable Cox's proportional survival analysis, using prespecified relevant variables known to be associated with adverse outcomes in these patients (a *P* value ≤0.1 was used as entry criteria). MV surgery was included as a time-dependent covariate in Cox's survival analysis. For each patient undergoing MV surgery, the analysis time was modeled so that only the person-time after MV surgery was included in the surgical group. The person-time before occurrence of MV surgery was included in the nonsurgical category. Hazard ratios with 95% confidence intervals were calculated. To ensure that proportional hazards assumption was not violated, graphical inspection of Schoenfeld residuals plotted against time was performed. Additionally, cumulative proportion of events as a function over time was obtained by Kaplan-Meier's method

and event curves were compared using the log-rank test. For relevant variables, we also assessed incremental reclassification of risk for adverse outcomes using net reclassification improvement (NRI). Statistical analysis was performed using SPSS (version 11.5; SPSS, Inc., Chicago, IL), Stata (version 10.0; StataCorp LP, College Station, TX), and R software (3.0.3; R Foundation for Statistical Computing, Vienna, Austria). A *P* value of <0.05 was considered significant.

## Results

Baseline characteristics are shown in Table 1. Patients with MLS MR comprised 20% of the total study population and were twice as likely to be women as in the HS group (53% versus 27%), were younger, and had less comorbidity at baseline. Baseline echocardiographic characteristics are shown in Table 2. In the MLS group, bileaflet prolapse was more common, whereas unileaflet prolapse was more frequently observed in the HS group. Only 6% of those with non-HS MR manifested flail leaflet versus 36% of those with HS MR. Mean VCW, mitral EROA, and regurgitant volume were higher in the HS versus MLS group. Baseline LV and LA size, RVSP, and tricuspid regurgitation severity were greater in the HS group at baseline, whereas LV and RV systolic function were similar.

Results of treadmill exercise echocardiography are shown in Table 2. The majority of the patients achieved >85% of

predicted maximal heart rate, terminating the stress test owing to generalized fatigue. There were no significant arrhythmias, syncope, or deaths during the treadmill exercise test. MLS MR patients had a greater endurance, as determined by METS, but not when age and gender corrected, as compared to HS patients. There were 110 (18%) patients who had poststress RVSP  $\geq 60$  mm Hg with a higher proportion in the HS subgroup, as compared to the MLS subgroup (20% versus 11%; *P*=0.009). Only 2 patients in the MLS group developed HS MR at peak stress.

## Follow-up Data

In total, 398 (65%) patients underwent MV surgery (360 or 90% MV repair and 38 or 10% MV replacement), with the median time to surgery (from the treadmill echocardiography) being 2 months (interquartile range [IQR], 1 to 12 months). All patients undergoing surgery met at least Class IIa indication according to guidelines.<sup>6</sup> A similar proportion of patients underwent MV surgery in HS versus MLS subgroups (323 or 66% versus 75 or 62%; *P*=0.2). Patients with HS MR had significantly shorter time to surgery than the MLS MR group (median 2 months, IQR 1 to 9 months versus 3 months, IQR 1 to 18 months; *P*=0.01).

In the total group, 71 patients (12%) had new-onset AF (excluding postoperative AF occurring within 30 days) during follow-up (no difference between surgical versus nonsurgical

**Table 1.** Baseline Characteristics of the Study Population

Variable	Total (n=609)	Mid-Late Systolic MR (n=122)	Holosystolic MR (n=487)	<i>P</i> Value
Age, y	59±13	53±12	60±14	<0.01
Gender, %				
Male	67	48	72	<0.01
Female	33	53	27	
Body mass index, kg/m <sup>2</sup>	26±4	25±4	26±4	0.3
Hypertension, %	47	37	49	<0.01
Diabetes mellitus, %	4	3	5	0.4
Coronary artery disease, %	12	6	14	0.01
Previous CHF, %	2	2	2	0.6
Previous stroke, %	3	1	3	0.2
Atrial fibrillation, %	13	7	15	<0.01
Additive Euroscore	3.9±2.6	4.2±2.7	2.8±1.9	<0.01
Pacemaker/defibrillator, %	2	1	3	0.2
Beta-blockers, %	31	36	30	0.1
ACE-I or ARB, %	37	26	39	<0.01
Aspirin, %	38	40	37	0.4

ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MR, mitral regurgitation.

**Table 2.** Resting and Exercise Echocardiographic Parameters of the Study Population

Variable	Total N=609	Mid-Late Systolic N=122	Holosystolic N=487	P Value
<b>Resting echocardiography</b>				
LV ejection fraction, %	58±5	58±5	58±5	0.5
Indexed LV end-diastolic dimension, cm/m <sup>2</sup>	2.7±0.6	2.7±0.6	2.9±0.6	0.002
Indexed LV end-systolic dimension, cm/m <sup>2</sup>	1.6±0.5	1.7±0.4	1.6±0.5	0.03
Left atrial area, cm <sup>2</sup>	26±7	25±6	27±7	0.003
<b>Mitral leaflet prolapse, %</b>				
Anterior	9	0	11	<0.001
Posterior	41	14	48	
Bileaflet	50	86	41	
Flail mitral valve, %	30	6	36	<0.001
<b>Mitral regurgitation %</b>				
III+	38	57	34	
IV+	62	43	66	<0.001
VCW, cm	0.85±0.2	0.80±0.2	0.87±0.2	<0.001
Duration of MR during systole, %	91±18	57±14	100±0	<0.001
Product of VCW and MR duration during systole	75±29	44±18	83±26	<0.001
Mitral effective regurgitant orifice area, cm <sup>2</sup>	0.48±0.3	0.41±0.2	0.49±0.3	<0.001
Mitral regurgitant volume, mL	68±37	48±25	70±37	<0.001
Normal right ventricular size, %	99	99	98	0.7
Normal right ventricular function, &	99	100	98	0.7
Resting RVSP, mm Hg	31±12	27±9	33±11	<0.001
<b>Tricuspid regurgitation, %</b>				
None	7	3	5	
Trivial-mild	77	84	76	0.02
Moderate to moderate-severe	16	10	19	
<b>Treadmill echocardiography</b>				
% achieving 85% predicted maximal heart rate	88	92	86	0.07
METS achieved	10±3	10.5±3	9.5±3	<0.001
<b>Age-gender-predicted METs, %</b>				
≤100%	27	23	28	
>100%	73	77	72	0.2
Poststress RVSP, mm Hg	46±17	44±13	48±16	0.004
Stress-induced ischemia, %	4	3	4	0.3
<b>Change in LV cavity size with stress, %</b>				
Decrease	91	91	89	
Unchanged	7	5	8	0.5
Increased	1.4	1	2	

LV indicates left ventricle; METs, metabolic equivalents; MR, mitral regurgitation; RVSP, right ventricular systolic pressure; VCW, vena contracta width.

groups). Also, there were an additional 23 (4%) patients who required pacemaker implantation and 8 (1%) with implantable cardioverter defibrillator implantation, respectively. The breakdown of New York Heart Association (NYHA) class at final

follow-up was as follows: 540 (89%) in Class I; 67 (11%) in Class II; 1 (0.2%) in Class III; and 1 (0.2%) in Class IV. There were no differences in late symptoms between HS and MLS subgroups. All patients had at least 1 follow-up at our

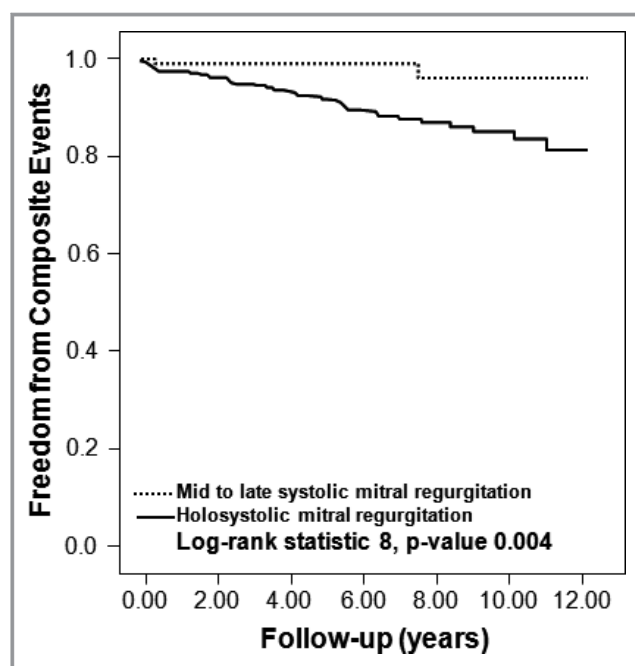
institution and the vast majority (90%) had more than 1 follow-up. Based on chart review, nonoperated patients have remained asymptomatic (defined as no further progression of NYHA class and/or new symptoms attributable to MR) at the time of last follow-up at our institution.

### Outcomes and Survival Data

During a follow-up of  $7.1 \pm 3$  years, 53 patients (9%) met the composite endpoint. At the time of death, no patient had a noncardiac condition that would result in their deaths. The breakdown of individual endpoints was as follows: 29 (5%) deaths and 25 (4%) patients with progression to CHF. In patients who developed multiple endpoints, the time to the first event was utilized as an event time cutoff (1 patient had CHF develop before his death, and so in the composite outcomes, that individual was counted as having had 1 event, ie, CHF and the censor date was at the onset of CHF). Additionally, there were 6 (1%) strokes and 6 (1%) transient ischemic attacks. The proportion of composite events between surgical and nonsurgical groups were similar ( $P=0.8$ ). In the surgical group, 3 patients had events before surgery. There were no deaths at 30-day postoperatively, whereas 1 patient had a stroke at day 29 postoperatively. A higher proportion of patients met the composite endpoint in the HS versus the MLS subgroup (49 or 10% versus 4 or 3%, log-rank statistic 8;  $P=0.004$ ; Figure 3). All 29 deaths occurred in the HS subgroups, whereas all 4 events in the MLS subgroup were development of CHF during follow-up.

The results of univariable and forward step-wise multivariable Cox's proportional hazard survival analysis are shown in Tables 3 and 4. The following parameters were predictive of adverse outcomes: HS MR; lower percentage of age- and gender-predicted METs achieved; higher resting RVSP; AF; and lower resting LVEF. When Euroscore was substituted in the multivariable analysis, instead of its individual variables, the results were similar. Neither MV surgery nor its timing from stress echocardiography impacted outcomes.

Subsequently, we evaluated the incremental value of MR duration and exercise capacity in risk stratification for outcomes, in addition to established variables. When MR duration (HS versus MLS) was added to the model that included additive Euroscore, mitral EROA, and presence/absence of flail leaflet, it significantly improved classification of risk (NRI, 0.17 [0.02 to 0.30];  $P=0.03$ ). The addition of percentage of age- and gender-predicted METs to the model that included additive Euroscore, mitral EROA, presence/absence of flail leaflet, and MR duration (HS versus MLS) significantly improved classification of risk (NRI, 0.53 [0.26 to 0.81];  $P<0.001$ ).



**Figure 3.** Kaplan-Meier's analysis in the study population, divided on basis of holosystolic versus mid-late systolic mitral regurgitation.

### Discussion

Our study has 2 main findings. First, MLS MR occurs in approximately 20% of asymptomatic patients with degenerative MR and is characterized by a higher prevalence in women, younger age, and less comorbidity and has a preponderance of bileaflet prolapse. Second, the presence of HS (rather than MLS) MR was independently associated with higher composite outcome of mortality and CHF, along with lower age- and gender-predicted exercise capacity, higher resting RVSP, lower resting LVEF, and AF. Incorporating MR duration and exercise capacity improves risk stratification, over standard clinical and echocardiographic (EROA and flail mitral leaflet) predictors. Worse outcome in HS MR patients was observed in spite of significantly shorter time to surgery in these patients. Whereas ejection fraction was equally preserved in both HS and MLS subgroups, patients with HS MR had a larger LA area and higher RVSP at rest and at peak exercise, indicative of a more severe volume and, possibly, pressure overload.

This is one of the largest studies to investigate the impact of systolic duration of MR and exercise echocardiography on outcomes of patients with significant myxomatous MR. A recent study has shown fewer cardiac events in patients with MLS, compared to HS MR.<sup>10</sup> However, this study had a much smaller sample size and included patients with generally lesser severities of MR who were only under medical management. As a result, the differences in outcomes after

**Table 3.** Univariable Cox's Proportional Hazards Survival Analysis for the Study Population

Variable	Univariable	
	Hazard Ratio	P Value
Age (per year increase)	1.09 [1.05 to 1.2]	0.001
Male gender	1.13 [0.62 to 2.07]	0.7
Body surface area	1.43 [0.43 to 4.76]	0.6
No hypertension	0.91 [0.51 to 1.61]	0.7
No diabetes mellitus	0.94 [0.24 to 2.71]	0.2
No hyperlipidemia	0.63 [0.34 to 1.16]	0.11
No obstructive coronary artery disease	0.45 [0.74 to 2.71]	0.2
No CHF	0.65 [0.74 to 2.65]	0.5
Atrial fibrillation/flutter	2.92 [1.46 to 5.86]	0.002
Beta-blockers	0.58 [0.30 to 1.10]	0.13
ACE inhibitors/ARBs	0.57 [0.31 to 1.14]	0.2
Additive Euroscore	1.38 [1.26 to 1.51]	<0.001
LV ejection fraction (per % increase)	0.93 [0.89 to 0.98]	0.003
Indexed LV end-systolic dimension (per cm/m <sup>2</sup> increase)	0.83 [0.42 to 1.63]	0.6
Left atrial area (per cm <sup>2</sup> increase)	1.40 [0.90 to 2.18]	0.1
Resting right ventricular systolic pressure (per mm Hg increase)	1.06 [1.04 to 1.08]	<0.001
Peak-exercise right ventricular systolic pressure (per mm Hg increase)	1.02 [0.96 to 1.06]	0.2
Mitral effective regurgitant orifice area	1.01 [1.005 to 1.08]	0.04
Mitral regurgitant volume	1.04 [1.01 to 1.07]	0.02
Quantified duration of mitral regurgitation in systole	1.31 [1.01 to 1.28]	0.03
Holosystolic vs mid-late systolic mitral regurgitation	6.11 [1.44 to 25.79]	0.02
Single vs bileaflet mitral prolapse	1.23 [0.80 to 1.92]	0.3
Flail mitral leaflet	0.9 [0.5 to 1.64]	0.6
No ischemia on stress echo	0.92 [0.53 to 1.59]	0.6
% age and gender predicted METs (per % increase)	0.98 [0.97 to 0.99]	0.004
Mitral valve surgery (time dependent covariate analysis)	0.70 [0.39 to 1.28]	0.2
Time to mitral valve surgery, months	1.00 [0.99 to 1.01]	0.8

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CHF, congestive heart failure; LV, left ventricle; METs, metabolic equivalents.

**Table 4.** Forward Step-wise Multivariable Cox's Proportional Hazards Survival Analysis for the Study Population

Variable	Hazard Ratio	P Value
Atrial fibrillation/flutter	2.59 [1.33 to 5.11]	0.01
LV ejection fraction (per % increase)	0.94 [0.89 to 0.98]	0.003
Resting right ventricular systolic pressure (per mm Hg increase)	1.05 [1.03 to 1.09]	0.003
Holosystolic vs mid-late systolic mitral regurgitation	4.99 [1.21 to 20.14]	0.03
% age and gender predicted METs (per % increase)	0.98 [0.97 to 0.99]	0.004

Chi-square for the model, 54;  $P < 0.001$ . The following predictors were considered for inclusion in the final model: baseline risk factors; medications; LV ejection fraction; LV and left atrial dimensions; mitral effective regurgitant orifice area; holosystolic versus mid-late systolic mitral regurgitation; single versus bileaflet prolapse; flail; ischemic stress response; % age- and gender-predicted METs; mitral surgery (as a time-dependent covariate); and timing of mitral surgery from the stress test. Because age and gender were included in the calculation of % predicted METs, they were not included in the multivariable model. LV indicates left ventricle; METs, metabolic equivalents.

mitral surgery remain unclear. Also, that study did not incorporate exercise capacity in risk stratification.

Previous reports have commented on significant differences in patient groups who had predominantly uni- versus bileaflet prolapse. These studies have suggested a greater proportion of women, lesser degree of flail, and less-severe regurgitation for equivalent symptoms in the bileaflet prolapse group,<sup>24–26</sup> similar to what was noted in the present study. Also, these studies suggest some fundamental biomechanical differences in MV morphology between uni- and bileaflet prolapse. However, none of these previous studies examined the effect of duration of MR on long-term outcomes, in patients with myxomatous MR and uni- versus bileaflet prolapse. The apparent lesser degree of MR noted in the article by Shah et al. may, in part, relate to a shorter duration of MR in the bileaflet population.<sup>25</sup>

Recent attention has been geared toward the importance of exercise capacity in risk stratification of asymptomatic MR patients. Poor exercise capacity is caused by LV dysfunction,<sup>13,27</sup> which itself ensues from chronic volume overload during the course of MR. It is also well known that LV dysfunction can progress, but remain undetected, with a preserved ejection fraction for a long time.<sup>28</sup> Therefore, a reduction in exercise capacity in MR patients should be sought and addressed. In the current study, we demonstrate a significant ability of exercise capacity to improve risk stratification in patients with significant MR, along with MR duration. Patients with HS MR that do not achieve >100% of their age- and gender-predicted METs fare significantly worse, as compared to the other subgroups. On the other hand, patients with MLS MR who achieve >100% of their age- and gender-predicted METs have a very low event rate during follow-up.

Previous reports, including ours, have demonstrated the potential utility of exercise testing in predicting outcomes of asymptomatic patients with MR.<sup>13–15,29</sup> However, some of these were much smaller studies where the endpoint was development of symptoms, rather than hard events. Unlike the current study, the previous report from our group did not incorporate MR duration into prognostic analysis.<sup>29</sup> Also, for the current study, EROA and regurgitant volume were remeasured in all patients. Similar to previous reports, other known factors portending poorer outcomes included reduced LVEF, AF, and pulmonary hypertension.<sup>3,30–32</sup>

We also demonstrate that there were no significant differences in the proportion of HS versus MLS MR patients undergoing MV surgery. Approximately two thirds of patients in each group eventually underwent MV surgery. However, despite the time to surgery being longer in patients with MLS MR, these patients still had better outcomes during follow-up. It can be postulated that decreased volume overload in

patients with MLS MR translates into slower disease progression and better outcomes. Although one would expect to also see less surgical intervention in MLS MR patients,<sup>10</sup> this was not observed in our study. This is most likely because the decision to perform MV surgery had been primarily based on instantaneous severity of MR and not its duration during systole. Indeed, different qualitative and quantitative criteria have been suggested by major cardiac societies to classify the severity of MR.<sup>4–6</sup> Most of the quantitative criteria, such as VCW and EROA, are based on an instantaneous assessment of regurgitation and do not take regurgitation duration into account.

Another point of discussion involves the potential assumption that HS MR is simply a result of sequential progression of MLS MR. Based on the pattern of mitral leaflet involvement in the current study, that assumption appears flawed. The vast majority of patients with MLS MR had bileaflet prolapse, whereas posterior leaflet prolapse accounted for the majority of patients in the HS subgroup. Also, there was no anterior leaflet prolapse in those with MLS MR. Furthermore, flail leaflet was significantly more common in the HS group. These findings raise the possibility that the underlying mechanism of regurgitation is different in the 2 subgroups. The impact of HS MR on outcome may relate not only to its effect on regurgitant volume, but also to other significant differences between the HS and MLS groups. Many characteristics of MLS MR patients are similar to patients with bileaflet prolapse (which constitute >80% of the MLS group). Mitral leaflets in patients with bileaflet prolapse are known to be longer, and have higher chordal strength and less flail, when compared to unileaflet prolapse leaflets.<sup>24</sup> However, a proportion of patients with MLS MR may progress to HS MR owing to the fact that dynamic changes in loading conditions may alter the duration of regurgitation.

The current study has the following potential limitations. This is a large observational study in a tertiary center and therefore not free of referral bias. However, the patients in the current study were similar to those in previously published data.<sup>9,13</sup> We only included asymptomatic patients with  $\geq$ III+myxomatous MR that underwent exercise echocardiography. Therefore, patients who have been more symptomatic at baseline are not included in our study. It should also be kept in mind that exercise capacity is the output of overall function of cardiovascular, respiratory, and musculoskeletal systems. Other possible etiologies of impaired exercise capacity could have played an important role in predicting outcomes in these patients. Because of the observational nature of the study, stage C/D CHF during follow-up was ascertained by chart review and not adjudicated by multiple blinded reviewers as part of a clinical events committee. Also, the current retrospective cohort study only assumes association, not causality.



## Conclusion

In patients with  $\geq$ III+myxomatous MR undergoing exercise echocardiography, HS MR, compared to MLS MR, was associated with higher composite rate of mortality and heart failure. Prospective studies are needed to ascertain the results of our observational study.

## Disclosures

Dr Gillinov reports being a consultant to Edwards Lifesciences, Abbott, and On-X. He has received honoraria from St. Jude's Medical and Intuitive Surgical companies. Others report no conflict of interest.

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