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Relation of Frequency and Severity of Mitral Regurgitation to Survival Among Patients With Left Ventricular Systolic Dysfunction and Heart Failure

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The goal of this study was to examine the frequency of mitral regurgitation (MR) in patients with left ventricular (LV) systolic dysfunction and to relate its presence and severity to long-term survival. Remodeling of the left ventricle after myocyte injury leads to a progressive change in LV size and shape, and it may lead to the development of MR. The frequency of MR and its relation to survival in patients with LV systolic dysfunction has not been completely characterized. We analyzed the histories, coronary anatomy, and degree of MR in patients with symptomatic heart failure and LV ejection fraction <40% who underwent cardiac catheterization between 1986 and 2000. Cox's proportional hazards modeling was used to assess the independent effect of MR on survival. Two thousand fifty-seven patients met study criteria; MR was common in this cohort (56.2%). Of patients with MR, 811 (70.1%) had mild (grades 1+ or 2+) and 345 (29.8%) had moderate or severe (grades 3+ or 4+) regurgitation. Survival rates at 1, 3, and 5 years were significantly lower in patients with moderate to severe MR versus those with mild or no MR (p <0.001). MR was found to be an independent predictor of mortality after multivariable analysis (hazards ratio 1.23, 95% confidence interval 1.13 to 1.34, p = 0.0001). This relation of MR and survival was present in those with ischemic and nonischemic cardiomyopathies. MR is common in patients with LV systolic dysfunction and heart failure. After adjusting for other clinical variables, the presence of MR independently predicted worsened survival.
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Mitral regurgitation (MR) is a common finding in patients with heart failure, and it often develops during progressive remodeling and dilation of the left ventricle. However, the association between the presence of varying grades of MR and survival in patients with heart failure has not been well characterized. The purpose of this analysis was to determine the frequency of MR in a large cohort of patients with LV systolic dysfunction and clinical heart failure, and to explore the relations between the presence and severity of MR and survival.

METHODS

Patient selection: We prospectively analyzed collected data from the Duke Cardiovascular Databank on patients who underwent diagnostic cardiac catheterization in the adult catheterization laboratory at Duke University Medical Center for the evaluation of clinical heart failure (New York Heart Association [NYHA] class II to IV). Patients with a LV ejection fraction <40% were included in this analysis, and those with the following clinical characteristics were excluded: myocardial infarction within 30 days of catheterization, moderate or severe valvular stenosis, significant (≥75%) left main stenosis, and known congenital heart disease. Patients who underwent previous valve surgeries were excluded. Baseline clinical variables were stored in the Duke Databank using methods previously described.[1]

Cardiac catheterization: Data from the index catheterizations were prospectively collected. Coronary angiography was performed using standard techniques. Stenotic lesions were graded subjectively by visual consensus of ≥2 experienced observers on an ordinal scale of 0%, 25%, 50%, 75%, 95%, or 100%. Significant coronary artery disease (CAD) was defined as ≥75% diameter stenosis of an epicardial coronary artery.[2] The extent of CAD was characterized by the traditional 1-, 2-, or 3-vessel disease classification.[3]

Biplane views were obtained during all ventriculograms. Angiographic LV ejection fraction and regional wall motion were determined by centerline regional wall motion analysis.[4] In the presence of excessive ventricular ectopy or catheter-induced MR, ventriculography was repeated until it was technically adequate. The interpretations of all ventriculography data were performed by ≥2 experienced observers. Patients were classified as having an ischemic cardiomyopathy using the modified criteria recently proposed by Felker et al.[5]

Assessment of MR: The degree of MR was graded visually by the following criteria: 0 = no systolic regurgitation of contrast into the left atrium; 1+ = minimal regurgitation that cleared rapidly with a sub-

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sequent beat; 2+ = moderate opacification of the left atrium that cleared within several beats; 3+ = intense opacification of the left atrium that became equal to that of the left ventricle; 4+ = dense opacification of left atrium to a greater degree than the left ventricle, with reflux of contrast material into the pulmonary veins.[6]

Clinical follow-up: Follow-up contact for survival status was conducted at 6 months and 1 year (and annually thereafter) using self-administered questionnaires and telephone follow-up for nonresponders. Patients not contacted through this mechanism had their vital status determined through a search of the National Death Index.[7] Survival status was completed for 99% of the patients.

Statistical analysis: Baseline characteristics are expressed as medians with interquartile ranges for discrete variables and as proportions for continuous variables. Comparisons among groups were made with Pearson's chi-square test for discrete variables and the Kruskal-Wallis test for continuous variables. Survival curves for various groups were constructed using the Kaplan-Meier method, and comparisons were made using the log-rank test. Cox's proportional hazards regression modeling was used to adjust for differences in demographic and clinical variables and to assess the independent effect of MR on survival. The prespecified variables that were candidates in the multivariable model were age, ejection fraction, race, history of angina, gender, diabetes mellitus, tobacco use, hypertension, congestive heart failure severity, ventricular gallop, peripheral vascular disease, cerebral vascular disease, noncardiac comorbidities, year of entry into the databank, and an ischemic etiology of cardiomyopathy. A stepwise selection process was used to determine significant predictors of outcome. We checked for interactions between MR grade and etiology of cardiomyopathy (ischemic vs nonischemic) and year of study entry. A p value ≤ 0.05 was considered statistically significant for all comparisons and analyses.

Before constructing the Cox model, we first examined the shape and strength of the relation between the grade of MR and survival through the use of a flexible model-fitting approach that involved a spline function (cubic polynomials).[8] This function was graphically examined to assess the implicit assumption with this regression model that the grade of MR was linearly related to the logarithm of the hazards ratio. The nonlinear relation between severity of MR and log hazard of death led us to transform our grading system of MR into 3 levels (0 = none; 1+ or 2+ = mild; 3+ or 4+ = moderate to severe) to best characterize the relation between MR and survival in this population.

RESULTS

Frequency of MR: Two thousand and fifty-seven patients met the study criteria between January 1, 1986, and December 31, 2000 (Figure 1). Median follow-up of patients in the cohort was 3.4 years (1.4, 7.1). Of the total population, 1,156 of 2,057 subjects had MR of any grade (56.2%). Of these patients, 811 (70.1%) had mild (grades 1+ or 2+) and 345 (29.8%) had moderate or severe (grades 3+ or 4+) regurgitation.

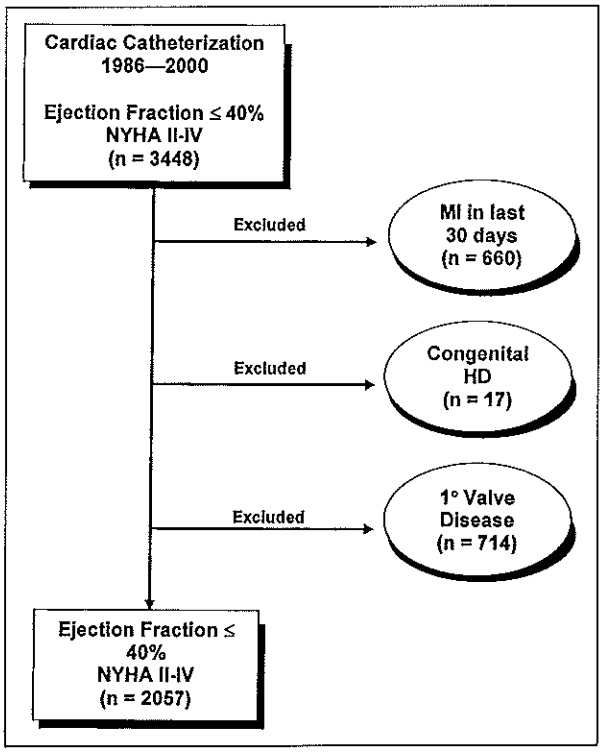

FIGURE 1. Identification of the study group. HD = heart disease; MI = myocardial infarction.

Baseline characteristics: Table 1 lists baseline characteristics for patients included in this analysis. Patients in our cohort ranged in age from 16 to 90 years (mean 60). Patients with more severe MR were more likely to be female ($p = 0.001$) and older ($p = 0.001$). Patients with MR also had lower ejection fractions ($p = 0.001$) and were more likely to have a ventricular gallop on physical examination ($p = 0.001$). Symptom severity, as measured by NYHA score, was worse in those with more severe grades of MR ($p = 0.001$).

Angiographic characteristics: The findings during coronary angiography are listed in Table 1. Almost 38% of patients with moderate or severe MR had no significant CAD; 28% of patients had 3-vessel CAD. The corresponding frequencies for the patients with mild MR were 39% and 30%, respectively.

Patients with more severe grades of MR were less likely to have an underlying ischemic cardiomyopathy compared with those with mild or no MR ($p = 0.04$). However, the frequency of previous myocardial infarction was not significantly different between those with and without MR ($p = 0.34$). Patients with more severe MR were less likely to have undergone a previous percutaneous coronary intervention ($p = 0.04$), but the frequency of coronary artery bypass grafting was not different between the comparison groups ($p = 0.696$).

Survival: The relation between the grade of MR and the log hazard of death is depicted in Figure 2. Sur-

TABLE 1 Baseline Characteristics

Characteristic	MR Grade 0 (n = 901)	1+ or 2+ (n = 811)	3+ or 4+ (n = 345)	p Value
Age (yrs)	60 (51, 68)	62 (53, 69)	65 (55, 72)	0.001
Body mass index	28 (25, 31)	26 (23, 30)	25 (23, 29)	0.001
Male (%)	71.1	59.7	49.3	0.001
Caucasian (%)	67.9	67.2	62.0	0.130
Angina pectoris (%)	68.6	65.4	60.0	0.015
Prior myocardial infarction (%)	37.4	34.7	33.6	0.337
Diabetes mellitus (%)	35.3	35.6	31.0	0.284
Hyperlipidemia (total cholesterol >200 mg/dl) (%)	39.0	39.5	31.6	0.029
Systemic hypertension (%)	63.8	63.9	58.6	0.001
Cigarette smoker (%)	64.2	62.4	53.9	0.003
Peripheral vascular disease (%)	14.4	16.7	14.2	0.371
Cerebrovascular disease (%)	13.2	12.7	11.0	0.580
Ischemic cardiomyopathy (%)	61.3	56.7	59.1	0.044
No. of coronary arteries narrowed >50% (%)				
0	36.9	38.7	37.7	0.029
1	14.1	17.4	12.8	
2	18.8	14.3	21.5	
3	30.3	29.6	28.1	
Prior coronary angioplasty (%)	15.1	12.0	10.4	0.044
Prior coronary bypass (%)	14.3	15.5	13.9	0.696
Ejection fraction (%)	28 (22, 34)	25 (19, 32)	25 (20, 33)	0.001
NYHA class (%)				0.001
II	30.6	24.7	19.4	
III	39.0	40.2	44.1	
IV	30.4	35.1	36.5	
Ventricular gallop (%)	24.8	34.4	41.2	0.001
Systolic blood pressure (mm Hg)	130 (114, 148)	130 (110, 147)	124 (110, 142)	0.004
Follow-up (yrs)	3.7 (1.7, 7.2)	3.3 (1.3, 6.9)	3.1 (1.3, 7.3)	0.374

Values are expressed as percent of patients.

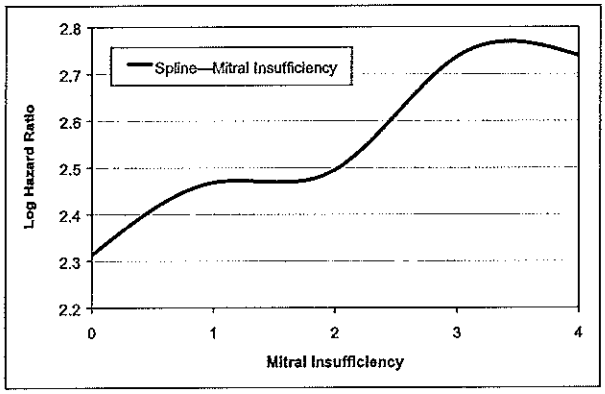

FIGURE 2. Relation between MR grade and hazard (risk) of death.

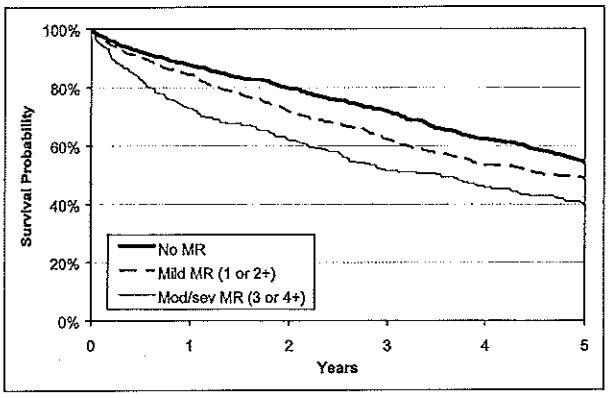

FIGURE 3. Unadjusted Kaplan-Meier survival estimates are shown. Patients with moderate or severe (Mod/sev) MR are represented by the *light line*, those with mild MR by the *dashed line*, and those with no MR by the *dark line*.

TABLE 2 Survival and Mitral Regurgitation (MR) Grade*

MR Grade	Survival Rate 1-year (n = 1, 587)	3-year (n = 977)	5-year (n = 623)
None (%)	87.6	71.8	54.2
Mild (1+ or 2+) (%)	84.4	62.3	48.7
Moderate or severe (3+ or 4+) (%)	72.9	51.4	39.9

*p <0.001.

vival rates at 1, 3, and 5 years were significantly lower in patients with moderate or severe MR versus those with mild or no MR (p <0.001; Table 2). Figure 3 shows unadjusted Kaplan-Meier survival curves according to the presence and grade of MR.

Univariable analysis was conducted to determine the clinical factors that were associated with survival (Table 3). Variables believed to have clinical importance, and those with p value <0.10 during univariate analysis, were included in the stepwise multivariable

TABLE 3 Unadjusted Associations Between Clinical Characteristics and Survival

Characteristic	Linear Regression Chi-Square	HR (95% CI)	p Value
Age (per 10 yrs)	171.9	1.409 (1.336–1.487)	0.0001
Ejection fraction (per 5% change)	21.5	0.916 (0.883–0.950)	0.0001
MR (increasing severity)	28.7	1.250 (1.153–1.356)	0.0001
Caucasian	3.4	1.131 (0.991–1.292)	0.0660
Angina pectoris	13.3	1.270 (1.115–1.447)	0.0003
Male sex (%)	6.611	1.177 (1.038–1.334)	0.0101
Systemic hypertension	9.410	1.212 (1.071–1.372)	0.0022
Ventricular gallop	5.586	1.166 (1.028–1.322)	0.0181
NYHA Class (↑)	13.130	1.151 (1.067–1.243)	0.0003
Diabetes mellitus	37.651	1.480 (1.308–1.673)	0.0001
Peripheral vascular disease	16.009	1.369 (1.174–1.596)	0.0001
Cerebrovascular disease	10.588	1.342 (1.131–1.592)	0.0011
Ischemic cardiomyopathy	71.535	1.720 (1.511–1.957)	0.0001
Previous coronary angioplasty	3.281	0.849 (0.708–1.017)	0.0701
Previous coronary bypass	2.642	1.150 (0.974–1.356)	0.1041

CI = confidence interval; HR = hazards ratio; ↑ = increasing.

TABLE 4 Cox Proportional Hazards Analysis: Independent Clinical Predictors of Survival

Characteristic	Wald Chi-Square	HR (95% CI)	p Value
Age (per 10 yrs)	144.0	1.426 (1.346–1.511)	0.0001
Ischemic cardiomyopathy	34.2	1.507 (1.314–1.729)	0.0001
Diabetes mellitus	30.6	1.432 (1.261–1.627)	0.0001
Ejection fraction (per 5-unit decrease)	27.7	1.115 (1.071–1.161)	0.0001
MR (increasing severity)	23.7	1.234 (1.134–1.343)	0.0001
Year of entry (per 1-yr increase)	19.1	0.962 (0.946–0.979)	0.0001
CHF severity (NYHA II–IV)	17.1	1.186 (1.094–1.287)	0.0001
Men	8.0	1.208 (1.059–1.378)	0.0048
Ventricular gallop	4.2	1.151 (1.006–1.317)	0.0407

CHF = congestive heart failure; other abbreviations as in Table 3.

model to determine those who were independently associated with survival.

Table 4 lists the results of the multivariable Cox proportional hazards regression model. The presence of MR at the time of diagnostic cardiac catheterization was an independent predictor of mortality (hazards ratio 1.23, 95% confidence interval 1.13 to 1.34, p = 0.0001). A 23% risk increase was associated with the change from no MR to mild MR, as well as the change from mild to moderate or severe MR. The adjusted survival curves show a progressive relation between increasing severity of MR grade and decreased survival (Figure 4).

We did not find a significant interaction between the MR grade and the etiology of the cardiomyopathy (p = 0.33). Thus, the risk associated with MR was the same in patients with or without ischemia after adjusting for other significant covariates. Figures 5 and 6 show survival curves stratified by the etiology of the cardiomyopathy. There was no interaction between MR and year of study entry (p = 0.4067).

Other independent predictors of mortality included age, an ischemic cardiomyopathy, diabetes mellitus, NYHA class, a later year of study entry, and a ventricular gallop during physical examination. A decreasing ejection fraction and male gender were also associated with an increased risk of death.

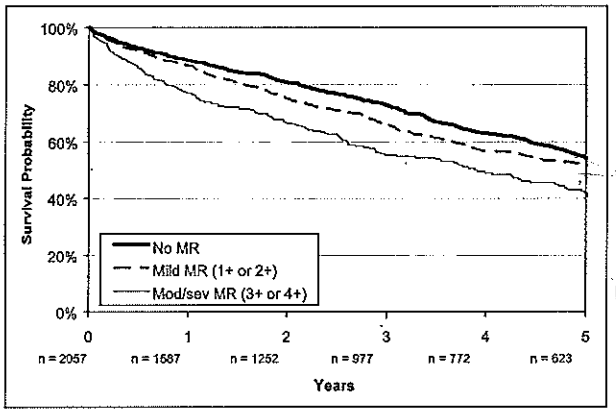

FIGURE 4. Adjusted survival estimates are shown. Patients with moderate to severe (Mod/sev) MR are represented by the *light line*, those with mild MR by the *dashed line*, and those with no MR by the *dark line*.

DISCUSSION

Our study represents the largest analysis to date that examines the frequency of MR in patients with LV systolic dysfunction and heart failure and its effect on survival. These data demonstrate that MR, as identified by ventriculography, is very common in this

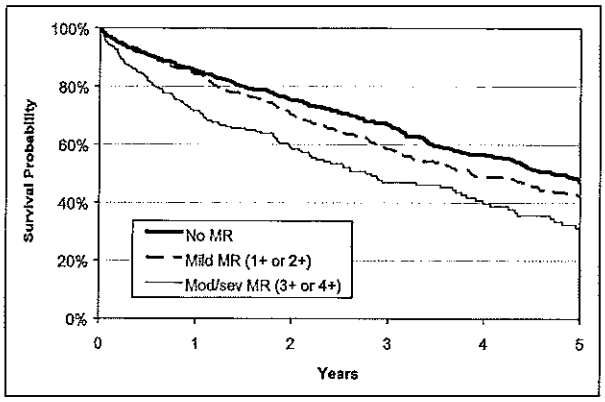

FIGURE 5. Adjusted survival estimates for patients with ischemic cardiomyopathies. Patients with moderate to severe (Mod/sev) MR are represented by the *light line*, those with mild MR by the *dashed line*, and those with no MR by the *dark line*.

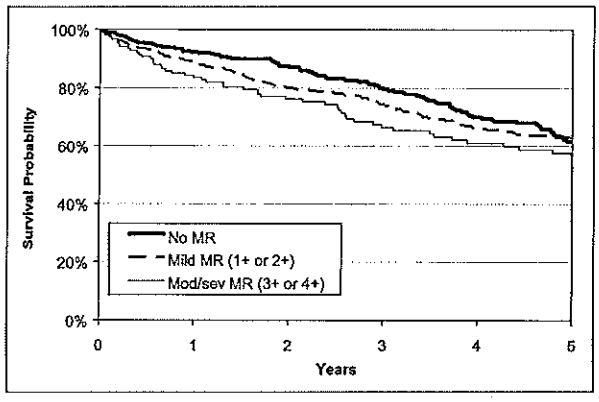

FIGURE 6. Adjusted survival estimates for patients with nonischemic cardiomyopathies. Patients with moderate to severe (Mod/sev) MR are represented by the *light line*, those with mild MR by the *dashed line*, and those with no MR by the *dark line*.

population; almost 60% of these patients have MR of any grade. Most patients in whom MR was identified had a mild (grade 1+ or 2+) degree of regurgitation. In the unadjusted analysis, patients with MR of any grade had significantly worse survival rates than those without. We found a dose–response relation between MR and survival, with more severe grades of regurgitation associated with significantly decreased survival rates compared with those with no or mild degrees of regurgitation (Figure 2). After multivariable adjustment for differences in these characteristics, the presence of MR remained an independent predictor of worsened survival in our population.

We identified a high frequency of MR in our study cohort. This finding has been previously reported.[9–10] These earlier investigations included small numbers of patients with advanced heart failure who were awaiting transplant and reported the frequency of severe MR only. Our cohort encompassed a wide spectrum of patients with heart failure with varying degrees of LV systolic dysfunction, CAD, and symptoms. Additionally, we reported the frequency of all grades of MR.

Patients with more severe grades of MR at ventriculography were more likely to have a ventricular gallop during the physical examination performed before catheterization compared with those with mild or no MR. The presence of a gallop is classically considered a hallmark of severe, chronic MR, although it does not necessarily indicate concomitant LV systolic dysfunction.[11] In our analysis, the presence of a gallop during the examination was independently related to worsened survival. A recent analysis reported the independent prognostic importance of an S_3 gallop in patients with heart failure.[12] These investigators did not report the frequency of MR in the study population. The presence of a gallop during the physical examination of a patient with LV systolic dysfunction may indicate the presence of underlying MR, partially explaining its relation to adverse clinical outcomes in this population. This association requires further study.

We identified MR as an independent predictor of worsened survival in patients with LV systolic dysfunction and symptomatic heart failure. There have been few reports that have identified this relation. Blondheim et al[13] studied 91 patients with a dilated cardiomyopathy to assess the frequency of MR and LV thrombi and their relation to survival. After a mean follow-up period of 32 months, patients with MR had a decreased survival compared with those without MR (22% vs 60%, $p < 0.005$). In a separate report, Conti and Mills[10] found that patients with severe dilated cardiomyopathy and advanced heart failure who lived <3 months after transplant listing were more likely to have severe MR compared with those who lived ≥3 months.[10]

Our investigation expands the findings of the previously mentioned studies. The 2 reports included <110 patients combined[10,13] and predominantly included patients with more advanced heart failure who were awaiting a transplant.[10] Our study cohort contained >1,100 patients, and our median follow-up time was 3.5 years. Multivariable analysis permitted assessment of the independent effect of various grades of MR on survival while controlling for other important variables that are known to influence outcome in patients with heart failure. We also obtained complete cardiac catheterization and coronary angiography data for all patients. This allowed us to precisely characterize the extent of CAD, the frequency of ischemic cardiomyopathy, and the prognostic importance of MR as it relates to the underlying etiology of LV systolic dysfunction.

In conclusion, we found that MR was common in patients with LV systolic dysfunction and heart failure. After adjusting for other important variables, there was a relation between the presence of MR and survival. The observed relation between MR and survival was progressive; the lowest survival rate was for patients with a moderate or severe degree of MR and was consistent in patients with ischemic and nonischemic cardiomyopathies.

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