

Left Atrial Size Is a Potent Predictor of Mortality in Mitral Regurgitation Due to Flail Leaflets

Results From a Large International Multicenter Study

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Background—Left atrium (LA) enlargement is common in organic mitral regurgitation (MR) and is an emerging prognostic indicator. However, outcome implications of LA enlargement have not been analyzed in the context of routine clinical practice and in a multicenter study.

Methods and Results—The Mitral Regurgitation International DAtabase (MIDA) registry enrolls patients with organic MR due to flail leaflets, diagnosed in routine clinical practice, in 5 US and European centers. We investigated the relation between LA diameter and mortality under medical treatment and after mitral surgery in 788 patients in sinus rhythm (64 ± 12 years; median LA, 48 [43 to 52] mm). LA diameter was independently associated with survival after diagnosis (hazard ratio, 1.08 [1.04 to 1.12] per 1 mm increment). Compared with patients with LA <55 mm, those with LA ≥ 55 mm had lower 8-year overall survival ($P < 0.001$). LA ≥ 55 mm independently predicted overall mortality (hazard ratio, 3.67 [1.95 to 6.88]) and cardiac mortality (hazard ratio, 3.74 [1.72 to 8.13]) under medical treatment. The association of LA ≥ 55 mm and mortality was consistent in subgroups. Similar excess mortality associated with LA ≥ 55 mm was observed in asymptomatic and symptomatic patients (P for interaction, 0.77). In patients who underwent mitral surgery, LA ≥ 55 mm had no impact on postoperative outcome ($P > 0.20$). Mitral surgery was associated with greater survival benefit in patients with LA ≥ 55 mm compared with LA <55 mm (P for interaction, 0.008).

Conclusions—In MR caused by flail leaflets, LA diameter ≥ 55 mm is associated with increased mortality under medical treatment, independent of the presence of symptoms or left ventricular dysfunction. (*Circ Cardiovasc Imaging*. 2011;4:473-481.)

Key Words: mitral valve regurgitation ■ flail leaflets ■ left atrium ■ prognosis

Mitral regurgitation (MR) is a progressive disease associated with high morbidity and mortality under conservative treatment.^{1,2} Guidelines^{3,4} recommend mitral surgery in patients with MR and overt symptoms, left ventricular (LV) dysfunction, pulmonary hypertension, or atrial fibrillation (AF) because these patients are at high risk of death and cardiac events under medical treatment.⁵⁻⁷ However, patients with “guideline surgical indications” may incur excess mortality even after successful surgery,⁵⁻⁷ and therefore, additional markers of risk are needed to better identify high-risk groups and define the optimal timing of surgery.

Clinical Perspective on p 481

Left atrium (LA) enlargement secondary to volume overload is common in chronic organic MR, reflecting both the

severity and the duration of MR.⁸ In chronic organic MR, LA enlargement is the expression of the regurgitated volume, the intrinsic compliance of the LA, and the associated LV function impairment.^{9,10} In contrast with LV dimensions and LV ejection fraction (EF), LA size is affected to a lesser degree by acute changes in preload or afterload and it therefore reflects the average effect of LA pressure over time.¹¹ Previous reports have shown that in the general population LA enlargement is predictive of death,¹²⁻¹⁴ incident heart failure,¹⁵ AF¹⁶ and stroke.¹³ Moreover, there is a close relation between LA enlargement and mortality in high-risk groups such as dilated cardiomyopathy,¹⁷ myocardial infarction,¹⁸ and after aortic or mitral¹⁰ valve surgery.

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In patients with organic MR, single-center studies suggested that LA size is a marker for subsequent AF.^{19–21} In regard to survival under medical treatment, pilot data suggest that LA enlargement measured by LA volume may be a useful predictor.²² However, LA diameter^{23,24} is currently of more widespread use than LA volume. Furthermore, generalizability of LA enlargement as a marker of MR outcome requires testing in large numbers of patients, diagnosed in routine practice and in a multicenter setting. The Mitral Regurgitation International DAtabase (MIDA) registry is an international database gathered to analyze the outcome of MR due to flail leaflets, and offers a unique opportunity to address this issue. Therefore, we sought to establish whether this simple measure of LA enlargement is predictive of mortality under medical treatment and after mitral surgery in a large cohort of patients with organic MR due to flail leaflets^{2,7} in sinus rhythm.

Methods

Study Design

The MIDA registry was previously described.^{2,7} Briefly, we merged the consecutive experience with MR due to flail leaflets of 5 centers, 4 tertiary centers in Europe and 1 center in the United States. The process of forming each center dataset involved retrospective identification of consecutive patients diagnosed with MR due to flail leaflets since inception of echocardiographic database. We obtained institutional review board authorizations prior to conducting the study. The study was conducted in accordance with institutional policies, national legal requirements, and the revised Helsinki Declaration.

Patients were screened for the study if they had degenerative MR with flail leaflet diagnosed by 2D echocardiography.² A comorbidity index summing the patient's comorbidities was calculated.²⁵ The registry currently includes 1158 patients. LA diameter was available in 1004 patients (87%). In 154 patients (13%), LA diameter was not measurable, due in general to morphotype. Given the independent effect of AF on LA enlargement, for this analysis we considered only patients in sinus rhythm at baseline (n=788).

Echocardiography

Transthoracic echocardiograms were performed within routine clinical practice, using standard methods.² LA diameter was measured in M-mode at end-systole in the parasternal long-axis view, according to the method proposed by the American Society of Echocardiography.²⁶ When M-mode measurement was not possible (oblique incidence), 2D measurement was performed. Severity of MR was assessed semiquantitatively on a scale from 1 to 4 by Doppler echocardiography.² Diagnosis of flail leaflet was based on the failure of leaflet coaptation, with rapid systolic movement of the involved leaflet tip in the left atrium.^{2,27}

Follow-Up

Follow-up collection was achieved for 760 patients (96%) up to 2006 or death. The main end point was overall survival after diagnosis under medical treatment. Other end points were cardiac mortality, overall survival encompassing medical and surgical treatment and postoperative survival in patients who underwent surgery. During follow-up, patients were monitored by their personal physicians. Events were ascertained by clinical interviews and/or by telephone calls to physicians, patients, and (if necessary) next of kin. Autopsy records and death certificates were consulted for attribution of causes of death.^{2,7}

Statistical Analysis

Continuous variables were expressed as mean value \pm 1 SD, and categorical variables were summarized as frequency percentages.

The relationship between continuous baseline variables and LA categories was explored using 1-way ANOVA or the Kruskal-Wallis test, as appropriate. Pearson χ^2 statistic or Fisher exact test were used to examine the association between categories of LA diameter and baseline categorical variables. The significance between the lowest LA category (LA <50 mm) and the others was examined if there was a significant difference across categories. Probability values were not adjusted for multiple comparisons and therefore are provided only for descriptive purposes.

For the analysis of outcome under conservative treatment, data were censored at the time of cardiac surgery, if eventually performed. The entire follow-up was used to analyze outcomes under conservative and surgical treatment. The effect of mitral surgery on outcome was analyzed as a time-dependent covariate using the entire follow-up. The survival time of patients lost to follow-up was censored at the date of last contact. The best prognostic LA diameter cutoff value for overall mortality was defined using receiver operating characteristic curve analysis according to the best sensitivity, specificity, and likelihood ratio. Overall mortality rates were estimated according to the Kaplan-Meier method and compared with a 2-sided log-rank test. Univariate and multivariable analyses of time to events were performed using Cox proportional hazards models with LA diameter as the predictor variable in continuous and categorical format. We did not use model-building techniques and entered in the models covariates considered of potential prognostic impact on an epidemiological basis. These covariates were: comorbidity index (including age), sex, symptoms, EF, and left ventricular end-systolic diameter (LVESD). We analyzed cardiac death in a Cox proportional hazards multivariable model while patients who died of noncardiac causes were censored (as nonevents) at the time of death. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated for cardiac death. Plots of cumulative hazard functions were used to graphically display death of cardiac causes. The proportional hazards assumption was confirmed using statistics and graphs based on the Schoenfeld residuals. Penalized smoothing splines (*P*-splines) were used to illustrate the association of LA diameter as a continuous variable and the risk of overall mortality under medical treatment.⁷

We conducted subgroup analyses to determine the homogeneity of the association of LA diameter and mortality. First, we estimated the effect of LA diameter on mortality in each subgroup, using a Cox univariate model, and then we formally tested for first-order interactions in Cox models entering interaction terms, separately for each subgroup. A significance level of 0.05 was assumed for all tests. All probability values are results of 2-tailed tests. Data were analyzed with SPSS 13.0 (SPSS Inc, Chicago, IL) and S-Plus 8.0 (Insightful Inc, Seattle, WA). Receiver operating characteristic curve analysis was performed using MedCalc for Windows version 11.3 (MedCalc Software, Mariakerke, Belgium). The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Baseline Characteristics

The baseline characteristics of the 788 patients with organic MR due to flail leaflets in sinus rhythm, overall and stratified by LA diameter <50 mm, 50 to 54 mm, and \geq 55 mm are presented in Table 1. Ninety-one percent of patients had grade 3 to 4 MR by Doppler echocardiography. Mean LA diameter was 47.7 ± 8.0 mm (median, 48 mm; interquartile range, 43 to 52 mm). Compared with patients with LA <50 mm, those with LA 50 to 54 mm and LA \geq 55 mm were more often male and had more severe symptoms at baseline but similar comorbidity index (Table 1). Patients with greater LA dilation had larger ventricular dimensions, lower EF, and higher systolic pulmonary artery pressure (Table 1).

Table 1. Baseline Characteristics of the Study Population by Left Atrium Diameter

Variable	All Patients (n=788)	LA Diameter			P
		<50 mm (n=477)	50 to 54 mm (n=172)	≥55 mm (n=139)	
Age, y	64.1±12.5	63.6±13.1	65.5±11.2	64.2±11.9	0.23
Male sex, % (n)	69.3% (546)	66.5% (317)	69.2% (119)	79.1% (110)*	0.017
Overt symptoms, % (n)	27.7% (218)	24.9% (119)	29.7% (51)	34.5% (48)*	0.04
NYHA class, % (n)					
I	42.0% (331)	45.3% (216)	39.5% (68)	33.8% (47)*	0.08
II	30.3% (239)	29.8% (142)	30.8% (53)	31.7% (44)	
III	21.0% (166)	18.2% (87)	22.1% (38)	29.5% (41)	
IV	6.6% (52)	6.7% (32)	7.6% (13)	5.0% (7)	
Medical history					
Coronary artery disease, % (n)	7.1% (56)	6.7% (32)	5.8% (10)	10.1% (14)	0.30
Hypertension, % (n)	34.2% (269)	35.1% (167)	33.3% (57)	32.4% (45)	0.81
Diabetes mellitus, % (n)	5.3% (42)	4.8% (23)	6.4% (11)	5.8% (8)	0.72
Dyslipidemia, % (n)	30.9% (242)	30.6% (145)	33.9% (58)	28.5% (39)	0.57
Peripheral vascular disease, % (n)	5.3% (42)	5.9% (28)	3.5% (6)	5.8% (8)	0.47
Chronic obstructive pulmonary disease, % (n)	8.1% (64)	9.2% (44)	6.4% (11)	6.5% (9)	0.37
Cerebrovascular disease, % (n)	2.5% (20)	2.7% (13)	2.9% (5)	1.4% (2)	0.66
Infective endocarditis, % (n)	9.3% (73)	8.8% (42)	10.5% (18)	9.4% (13)	0.81
Charlson Comorbidity Index	2.9±1.8	2.8±1.8	3.0±1.8	3.1±1.9	0.10
Echocardiographic data					
LVEDD, mm	59.3±7.2	57.3±6.3	60.5±7.3†	64.7±7.0†	<0.001
LVESD, mm‡	35.5±6.7	34.3±6.1	35.8±6.6*	39.7±7.2†	<0.001
Ejection fraction, %	65.9±9.2	66.6±8.8	65.9±9.8	63.9±9.9*	0.011
Systolic pulmonary artery pressure, mm Hg§	42.0±14.4	39.5±12.9	41.9±13.3	49.2±17.3†	<0.001
Medical therapy, % (n)					
Angiotensin-converting enzyme inhibitors	47.3% (371)	46.2% (220)	45.9% (78)	52.5% (73)	0.39
β-Blockers	19.7% (155)	20.6% (98)	17.1% (29)	20.1% (28)	0.61
Diuretics	37.0% (290)	34.0% (161)	38.2% (65)	46.0% (64)*	0.032

LA indicates left atrium; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; and NYHA, New York Heart Association.

*P<0.05, individual category versus LA <50 mm.

†P<0.001, individual category versus LA <50 mm.

‡LVESD missing in 72 patients.

§Systolic pulmonary artery pressure missing in 415 patients.

||Charlson Comorbidity Index includes age.

Outcome With Medical Treatment

All-Cause Mortality

Seventy-two deaths were recorded during follow-up under conservative treatment. Eight-year survival was similar in patients with LA <50 mm and patients with LA 50 to 54 mm (P=0.27; Figure 1). Patients with LA 55 to 59 mm displayed lower 8-year survival compared with patients with LA <50 mm (P<0.001) and patients with LA 50 to 54 mm (P=0.013, Figure 1). LA enlargement >60 mm was not associated with poorer 8-year survival compared with LA 55 to 59 mm (P=0.70). Eight-year survival rate was higher for patients with LA <55 mm compared with patients with LA ≥55 mm (Figure 2A).

On multivariable analysis, after adjustment for comorbidity index, sex, symptoms, EF, and LVESD, LA diameter was independently associated with overall mortality (Table 2).

The character of the relationship between LA diameter and the risk of overall mortality under conservative treatment was estimated using spline functions for LA diameter (Figure 3). On multivariable analysis, there was no increase in mortality risk with increasing LA diameter when it remained <55 mm (adjusted HR, 1.05 [0.98 to 1.11] per 1-mm LA diameter increment; P=0.18). With LA ≥55 mm, there was a significant increase in mortality risk with increasing LA diameter (adjusted HR, 1.03 [1.01 to 1.07] per 1-mm LA increment; P=0.04). Compared with patients with LA <50 mm, those with LA 50 to 54 mm did not display excess mortality risk (adjusted HR, 1.39 [0.63 to 3.09]; P=0.42). The risk of all-cause mortality under medical treatment was significantly increased for patients with LA 55 to 59 mm and patients with LA ≥60 mm (adjusted HR, 2.91 [1.31 to 6.46]; P=0.009 for LA 55 to 59 mm versus LA <50 mm, and, respectively,

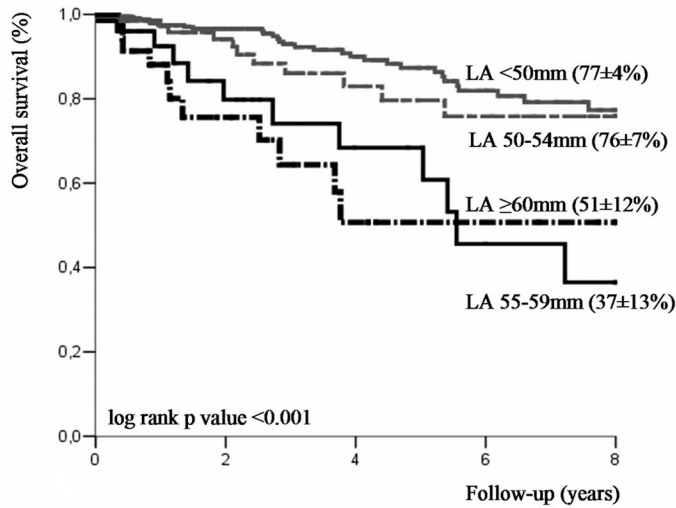


Figure 1. Overall survival by left atrium (LA) diameter (<50 mm; 50 to 54 mm; 55 to 59 mm; ≥60 mm) under conservative treatment.

Patients at risk

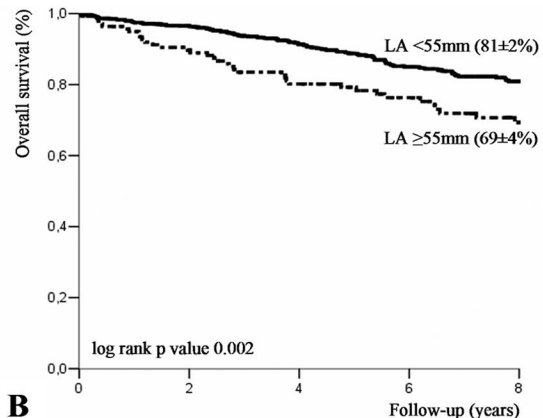
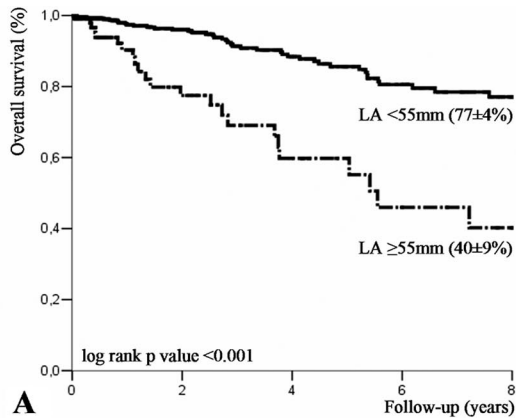
<50mm	477	194	114	68	36
50-54mm	172	54	26	18	11
55-59mm	75	18	11	5	3
≥60mm	64	15	7	4	2

adjusted HR, 6.94 [2.93 to 16.5]; *P*<0.001 for LA ≥60 mm versus LA <50 mm).

Death of Cardiac Causes

During conservative follow-up, 49 deaths of cardiac causes occurred. Causes of death were LV dysfunction (n=31, 63.2%), sudden death (n=12, 24.5%), thromboembolism (n=2, 4.1%), myocardial infarction (n=2, 4.1%), infective endocarditis (n=1, 2.0%), and aortic aneurysm rupture (n=1, 2.0%). After adjustment for comorbidity index, sex, symptoms, EF, and LVESD, LA diameter was independently predictive of death of cardiac causes (Table 2, Figure 4A).

There was a significant increase in cardiac mortality with increasing LA when it was ≥55 mm (HR, 1.04 [1.02 to 1.08] per 1-mm LA diameter increment; *P*=0.03) but not when it remained <55 mm (HR, 1.07 [0.98 to 1.18] per 1-mm LA diameter increment; *P*=0.10). Compared with patients with LA <50 mm, the risk of death of cardiac causes increased for patients with LA 55 to 59 mm and patients with LA ≥60 mm (adjusted HR, 3.09 [1.15 to 8.36], *P*=0.026 for LA 55 to 59 mm versus LA <50 mm, and adjusted HR, 7.31 [2.51 to 21.4]; *P*<0.001 for LA ≥60 mm versus LA <50 mm). Outcome was comparable for patients with LA <50 mm and patients with LA 50 to 54 mm (adjusted HR, 1.59 [0.58 to 4.33], *P*=0.36).



Patients at risk

<55mm	649	248	140	86	48
≥55mm	139	33	18	9	5

Patients at risk

<55mm	649	552	405	317	210
≥55mm	139	119	96	74	52

Figure 2. Overall survival according to left atrium (LA) diameter (<55 and ≥55 mm) under conservative treatment (A) and with medical and surgical treatment (B). A, Analysis of survival under conservative treatment took into account the overall follow-up for patients who had only medical therapy and preoperative follow-up for patients who were operated on (censored at surgery). B, Analysis of survival with medical and surgical treatment took into account the entire follow-up.

Table 2. Relative Risk of Overall Death and Death of Cardiac Causes Associated With Left Atrium Diameter

	Medical Treatment				Medical and Surgical Treatment*			
	Overall Death		Cardiac Death		Overall Death		Cardiac Death	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
LA diameter ≥55 mm								
Model 1	3.22 (1.92–5.43)	<0.001	3.60 (1.92–6.76)	<0.001	1.91 (1.33–2.74)	<0.001	1.89 (1.17–3.05)	0.009
Model 2	2.69 (1.57–4.60)	<0.001	2.84 (1.46–5.49)	0.002	1.76 (1.22–2.54)	0.002	1.69 (1.03–2.74)	0.03
Model 3	3.67 (1.95–6.88)	<0.001	3.74 (1.72–8.13)	0.001	1.78 (1.19–2.67)	0.005	1.66 (0.96–2.85)	0.06
Per 1-mm increment in LA diameter								
Model 1	1.07 (1.04–1.11)	<0.001	1.09 (1.05–1.13)	<0.001	1.04 (1.02–1.06)	<0.001	1.05 (1.02–1.08)	<0.001
Model 2	1.06 (1.03–1.09)	<0.001	1.08 (1.04–1.12)	<0.001	1.03 (1.01–1.05)	0.001	1.04 (1.02–1.07)	0.002
Model 3	1.08 (1.04–1.12)	<0.001	1.09 (1.04–1.15)	0.001	1.03 (1.01–1.06)	0.004	1.04 (1.00–1.07)	0.01

CI indicates confidence interval; EF, left ventricular ejection fraction; HR, hazard ratio; LA, left atrium; and LVESD, left ventricular end-systolic diameter.

Model 1: Adjusted for comorbidity index (includes age).

Model 2: Adjusted for comorbidity index, sex, symptoms, and EF.

Model 3: Adjusted for comorbidity index, sex, symptoms, EF and LVESD (missing in 72 patients).

*Analysis of outcome with medical and surgical treatment included the above-mentioned covariates and surgery as time-dependent covariate.

Subgroup Analysis

The association of LA ≥55 mm and all-cause mortality was consistent in subgroups of patients with MR (Figure 5). There were no significant interactions between LA ≥55 mm and any of the subgroups.

Patients in New York Heart Association (NYHA) class I at baseline with LA <55 mm had better outcome compared with the group with LA ≥55 mm (8-year overall survival: 83±4% versus 57±15%, P=0.032). After adjustment for covariates, LA ≥55 mm was independently predictive of overall mortality (adjusted HR, 2.40 [1.03 to 5.63]; P=0.044) and death of cardiac causes (adjusted HR, 3.42 [1.09 to 10.7]; P=0.035). The effect of LA ≥55 mm on overall mortality was similar in asymptomatic and symptomatic MR patients at baseline (P for interaction, 0.77).

In patients with EF <60% at baseline, 8-year survival rate was significantly higher for patients with LA <55 mm compared with patients with LA ≥55 mm (71±10% versus 8±7%; P<0.001). The risk of cardiac death was greater with

LA ≥55 mm compared with LA <55 mm (HR, 4.07 [1.46 to 11.4]; P=0.007). Patients with normal EF and LA <55 mm displayed better 8-year overall survival compared with the group with LA ≥55 mm (78±4% versus 63±12%; P=0.005). In this subgroup, patients with LA ≥55 mm had also increased risk of cardiac death compared with LA <55 mm (HR, 3.62 [1.71 to 7.67]; P=0.001).

The prognostic value of baseline LA diameter ≥55 mm was unaltered after excluding patients presenting with symptoms (NYHA class II-IV), reduced EF (<60%) and left ventricular dilation (LVESD ≥40 mm). In this subgroup of 222 patients without surgical indication at baseline, baseline LA ≥55 mm was associated with lower overall survival (55±20% versus 88±4%; P=0.034) and greater risk of cardiac death (HR, 6.32[1.57 to 25.5]; P=0.01).

Outcome With Medical and Surgical Treatment

Mean duration of follow-up with medical and surgical treatment was 6.2±3.9 years (median, 5.9; interquartile range, 2.8 to 9.2 years). In 29% of patients (n=225), treatment was solely medical, whereas 71% of patients (n=563) underwent mitral valve surgery. Mean time interval between baseline echocardiography and mitral surgery was 1.3±2.3 years (median, 0.2; interquartile range, 0.07 to 1.2 years). Valve repair was performed in 449 patients (80%) and valve replacement in 114 patients (20%).

During follow-up with medical and surgical treatment, 155 deaths were recorded. Eight-year survival rate was higher for patients with LA <55 mm compared with patients with LA ≥55 mm (Figure 2B). LA diameter was independently predictive of mortality (with medical and surgical treatment) in both continuous and categorical format (Table 2). Death of cardiac causes was recorded in 90 cases. On multivariable analysis, LA ≥55 mm was also predictive of cardiac death (Table 2 and Figure 4B).

Postoperative Outcome

In patients who underwent mitral surgery (n=563), mean postoperative follow-up was 4.1±4.0 years (median, 3.2;

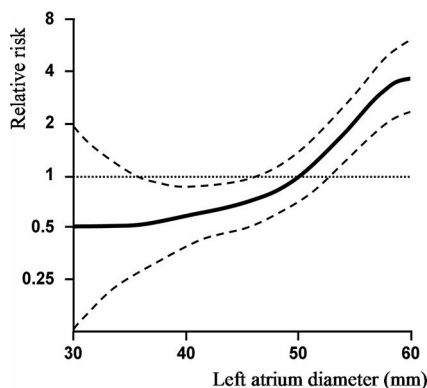


Figure 3. Relationship between left atrium (LA) diameter and the risk of overall mortality under conservative treatment. Hazard ratio (solid line) and 95% confidence intervals are estimated in a Cox model, with LA diameter represented as a spline function and adjusted for comorbidity index, sex, symptoms, and ejection fraction. The horizontal line corresponds to a hazard ratio of 1.00.

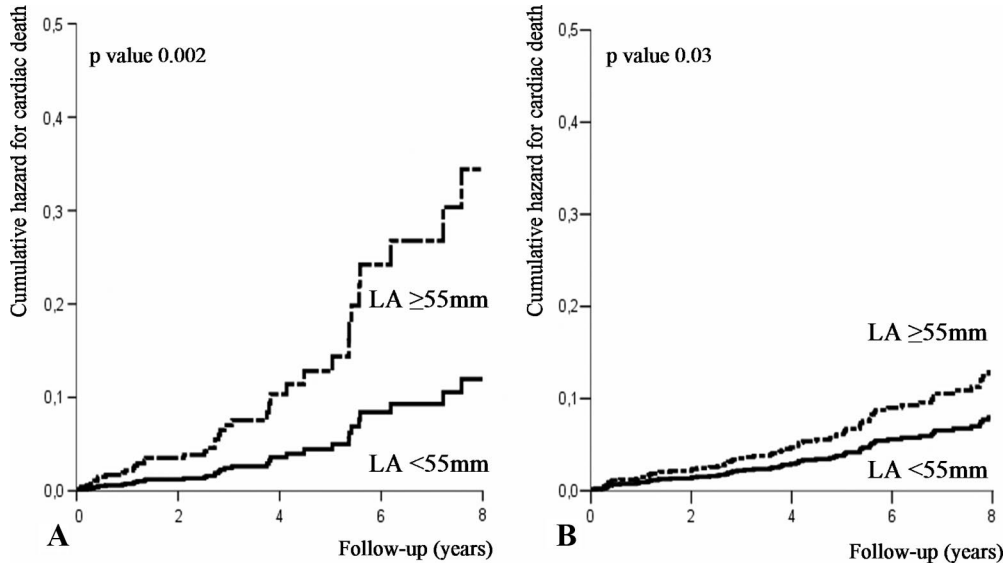


Figure 4. Cumulative hazard functions plots for cardiac death in patients with left atrium (LA) diameter <55 mm and ≥ 55 mm under conservative treatment (A) and with medical and surgical treatment (B). Explanatory note: See Figure 2.

interquartile range, 0 to 7.1 years). The baseline characteristics of patients who underwent surgery during follow-up and of patients who were treated medically are presented in Table 3. Compared with surgical patients, patients who were treated medically were older and had milder symptoms and less severe markers of volume overload (Table 3). On univariate analysis, LA diameter was not associated with postoperative death (HR, 1.14 [0.68 to 1.91] for LA ≥ 55 mm versus LA < 55 mm; $P=0.62$, and HR, 1.01 [0.97 to 1.03] per 1 mm LA increment; $P=0.97$) and death of cardiac causes (HR, 0.79 [0.35 to 1.78] for LA ≥ 55 mm versus LA < 55 mm; $P=0.57$, and HR, 1.00 [0.96 to 1.04] per 1-mm LA increment; $P=0.94$). After adjustment for covariates, LA ≥ 55 mm was still not a predictor of postoperative death (adjusted HR, 1.09 [0.63 to 1.88]; $P=0.77$) and death of cardiac causes (adjusted HR, 0.79 [0.34 to 1.84]; $P=0.59$).

On multivariable analysis, surgery was associated with improved overall survival (adjusted HR, 0.49 [0.31 to 0.78]; $P=0.003$) and survival free of cardiac death (adjusted HR, 0.37 [0.20 to 0.69]; $P=0.002$). The survival benefit after

surgery was greater in patients with LA ≥ 55 mm (adjusted HR, 0.12 [0.07 to 0.22]; $P<0.001$) compared with patients with LA < 55 mm (adjusted HR, 0.52 [0.31 to 0.85]; $P=0.009$; P for interaction, 0.008).

Discussion

In this large international cohort of patients with MR due to flail leaflets in sinus rhythm, LA diameter was a strong predictor of outcome under medical treatment. The effect of LA diameter on outcome was powerful and remained valid after adjustment for factors known as major determinants of prognosis such as age, comorbidity, symptoms, and LV function. Thus, LA diameter ≥ 55 mm was associated with more than 3-fold increase in the risk of all-cause mortality and risk of cardiac death under medical treatment. During follow-up with conservative treatment, the mortality risk associated with LA ≥ 55 mm was not significantly different in patients with LV dysfunction and patients with normal EF at baseline. Moreover, asymptomatic patients with LA ≥ 55 mm incurred excess mortality under medical treatment

Subgroup	HR (95% CI); p	p for interaction	
Age	≥ 75 years	3.22 (1.66 – 6.29); 0.001	0.29
	< 75 years	5.34 (2.52 – 11.3); <0.001	
NYHA class	II-IV	3.53 (1.89 – 6.60); <0.001	0.77
	I	3.16 (1.41 – 7.11); 0.005	
EF	$< 60\%$	6.42 (2.67 – 15.5); <0.001	0.06
	$\geq 60\%$	2.39 (1.22 – 4.69); 0.01	
LVESD	$< 40\text{mm}$	4.78 (2.42 – 9.45); <0.001	0.31
	$\geq 40\text{mm}$	2.32 (0.84 – 6.44); 0.11	

Figure 5. Hazard ratios and 95% confidence intervals for overall mortality associated with left atrium diameter ≥ 55 mm in subgroups of patients under conservative treatment. CI indicates confidence interval; EF, left ventricular ejection fraction; HR, hazard ratio; LVESD, left ventricular end-systolic diameter; and NYHA, New York Heart Association.

Table 3. Comparison Between Patients Who Had an Exclusive Medical Treatment During Follow-Up and Patients Who Underwent Surgery

Variable	Patients Treated Medically (n=225)	Operated Patients (n=563)	P
Age, y	66.9±14.6	62.9±11.4	<0.001
Male sex, % (n)	68.0% (153)	69.8% (393)	0.62
Overt symptoms, % (n)	13.8% (31)	33.2% (187)	<0.001
NYHA class, % (n)			
I	56.9% (128)	36.1% (203)	<0.001
II	29.3% (66)	30.7% (173)	
III	12.9% (29)	24.3% (137)	
IV	0.9% (2)	8.9% (50)	
Medical history			
Coronary artery disease, % (n)	9.8% (22)	6.0% (34)	0.10
Hypertension, % (n)	33.3% (75)	34.5% (194)	0.74
Diabetes mellitus, % (n)	6.3% (14)	5.0% (28)	0.47
Dyslipidemia, % (n)	25.3% (57)	32.9% (185)	0.045
Peripheral vascular disease, % (n)	7.1% (16)	4.6% (26)	0.23
Chronic obstructive pulmonary disease, % (n)	8.9% (20)	7.8% (44)	0.61
Cerebrovascular disease, % (n)	3.1% (7)	2.3% (13)	0.51
Infective endocarditis, % (n)	10.7% (24)	8.7% (49)	0.39
Charlson comorbidity index	3.3±2.1	2.8±1.7	0.001
Echocardiographic data			
LA diameter	45.7±7.9	48.9±7.9	<0.001
LVEDD, mm	57.1±6.9	60.2±7.1	<0.001
LVESD, mm	34.5±6.7	35.9±6.7	0.01
Ejection fraction, %	66.8±8.9	63.9±9.8	<0.001
Systolic pulmonary artery pressure, mm Hg	42.3±14.3	41.9±14.5	0.82
Medical therapy, % (n)			
Angiotensin-converting enzyme inhibitors	43.1% (97)	48.7% (274)	0.14
β-Blockers	20.9% (47)	19.2% (108)	0.61
Diuretics	38.2% (86)	36.2% (204)	0.62

LA indicates left atrium; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; and NYHA, New York Heart Association.

compared with patients with LA <55 mm. Although LA ≥55 mm was a potent marker of risk under conservative treatment, it did not significantly influence postoperative outcome of patients who underwent surgery and mitral surgery was associated with marked mortality reduction, especially in patients with LA ≥55 mm.

LA enlargement and remodeling in various cardiac conditions are mainly the consequence of volume overload, as in valvular regurgitation⁸ or pressure overload reflecting increased LV filling pressures.^{28,29} In chronic organic MR, LA enlargement is the response to the regurgitated volume, reflecting both the severity and the duration of MR.⁸ However, LA size may be influenced by the intrinsic compliance of the LA and by the associated LV diastolic impairment.^{8–10}

In contrast with LV dimensions and EF, LA size is affected to a lesser degree by acute changes in preload or afterload and it therefore reflects the average effect of LA pressure over time.¹¹ Chronically elevated LA pressures lead to morphological abnormalities in the LA wall⁸ and translate into increased neurohormonal activation and elevated pulmonary pressures.²¹ In the present study, patients with increased LA diameter experienced more severe symptoms and had significant LV dilation, lower EF, and increased pulmonary pressures. Thus, LA enlargement in organic MR appears to be a marker of more advanced disease.

Numerous reports demonstrated that in the general population, LA enlargement is predictive of death,^{12–14} incident heart failure,¹⁵ AF,¹⁶ and stroke.¹³ Moreover, in high-risk groups such as dilated cardiomyopathy¹⁷ and myocardial infarction,¹⁸ LA enlargement represents a factor associated with increased risk of death. In organic MR there are limited data on the prognostic implications of LA enlargement.^{10,19,21,22,27} Thus, LA enlargement has been shown to predict the occurrence of AF^{19–21} and heart failure.²⁷ In a study of 176 patients with symptomatic chronic MR who underwent mitral valve replacement, Reed et al¹⁰ reported LA size index, calculated by multiplying the maximal transverse and longitudinal LA dimensions in the apical 4-chamber view as an independent predictor of cardiac-related mortality after surgery. Messika-Zeitoun et al²¹ demonstrated an independent association between LA volume and a combined end point of death or mitral surgery in patients with organic MR in sinus rhythm. In a recent single-center pilot study²² including patients with organic MR of different etiologies, patients with indexed LA volume ≥60 mL/m² incurred excess mortality. Nevertheless, LA diameter is an easily measurable parameter of LA enlargement, currently of more widespread use than LA volume. Moreover, LA diameter is always recorded in clinical practice. The current study demonstrates that in patients with chronic organic MR under medical treatment, LA diameter is associated with excess all-cause mortality and cardiac mortality with a risk of death increasing progressively after the threshold of 55 mm. The pejorative effect of LA ≥55 mm was constantly observed in subgroups of MR patients. The judgment on high risk using LA diameter is therefore simple, feasible in all centers, and is confirmed by this multicenter study including a homogenous population of patients with organic MR due to flail leaflets amenable to valve repair.

The timing of surgery in MR is still debated, especially in asymptomatic patients^{1,2,30} and it has been shown that symptomatic patients and patients with overt LV dysfunction incur excess mortality even after successful surgery.^{1,2,5,7} Our results show that LA diameter is a marker of increased risk of death under conservative treatment and that it does not affect postoperative survival of patients undergoing surgery. The evaluation of LA size should therefore be systematically performed and considered when discussing surgery together with LV dimensions, EF, and symptoms.

A limitation of the present study was that clinical and nonechocardiographic data were obtained by review of medical records.² Our analysis is based strictly on the LA long-axis dimension, which is not always reflective of LA

enlargement and does not take into account the 3D geometry of the LA. Although in MR both LA diameter and LA volume are individually predictive of AF, LA volume displays higher predictive power for the occurrence of AF than LA diameter.²¹ LA volume was not available in the MIDA registry and therefore we could not ascertain its incremental prognostic value on survival over that of LA diameter. Because all patients in this registry had flail leaflet, the full spectrum of MR severity was not represented. In patients with severe MR who do not have a flail leaflet, there might be doubt as to whether MR is truly severe or not. In such patients, LA enlargement might also be a marker of higher risk and help decision-making. In the present study, patients were followed by their individual physicians. It is possible that some patients did not undergo mitral valve surgery despite having an indication for surgery during follow-up. Unfortunately, this information was not available in the MIDA registry. The number of events in the subgroup of asymptomatic patients with MR was small and results must be cautiously interpreted, in particular with regard to potential implications for surgery in asymptomatic patients. Finally, the issue of superiority of surgery over medical treatment in severe organic MR is beyond the scope of this analysis and should be based on randomized data.

Clinical Implications

This study, based on a large international multicenter database, shows that LA diameter is independently predictive of survival in patients with chronic organic MR due to flail leaflets in sinus rhythm under medical treatment. The risk of all-cause death and death of cardiac causes after diagnosis increases progressively with LA diameter above the 55-mm threshold. The association between LA diameter ≥ 55 mm and outcome is independent of the presence of factors such as symptoms and LV function. Surgery is particularly beneficial with LA ≥ 55 mm and does not imply excess postoperative mortality. LA diameter represents therefore a simple and easily obtainable echocardiographic measurement that might improve risk stratification in chronic organic MR.

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Disclosures

None.

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CLINICAL PERSPECTIVE

LA enlargement is common in chronic MR and is emerging as an important prognostic marker. However, the outcome implications of LA enlargement have not been analyzed in the context of routine clinical practice and in a multicenter study. The present analysis of the MIDA registry aimed to establish whether LA diameter, a simple measure of LA enlargement, is predictive of mortality under medical treatment and after mitral surgery in patients with organic MR due to flail leaflets. The relation between LA diameter and mortality was studied in 788 patients in sinus rhythm followed for 6.2 ± 3.9 years. LA diameter was independently associated with survival after diagnosis (HR, 1.08 [1.04 to 1.12] per 1-mm increment). The optimal cutoff value for prediction of mortality identified by receiver operating characteristic curve analysis was 55 mm. LA diameter ≥ 55 mm was associated with more than 3-fold increase in the risk of overall and cardiac mortality under medical treatment. The association of LA diameter ≥ 55 mm and mortality was consistent in subgroups of patients with MR and similar excess mortality was observed in asymptomatic and symptomatic patients. In patients who underwent mitral surgery, LA diameter ≥ 55 mm had no independent impact on postoperative outcome. Our findings show that LA diameter is a simple measurement that might improve risk stratification and decision making in chronic organic MR. LA diameter ≥ 55 mm is associated with increased mortality under medical treatment, independent of the presence of symptoms or left ventricular dysfunction.

Left Atrial Size Is a Potent Predictor of Mortality in Mitral Regurgitation Due to Flail Leaflets: Results From a Large International Multicenter Study

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