ESC European Society of Cardiology

European Journal of Heart Failure (2024)
doi:10.1002/ejhf.3393

SHORT REPORT

Indexing left ventricular end-systolic dimension to body size: Association with mortality in patients with degenerative mitral regurgitation

Christophe Tribouilloy[1,2]*, Dan Rusinaru[1,2], Francesco Grigioni[3], Jean-François Avierinos[4], Jean-Louis Vanoverschelde[5], Giovanni Benfari[6], Francesca Bursi[7], Andrea Barbieri[8], Yohann Bohbot[1,2], Benjamin Essayagh[6,9], Hector Michelena[6], and Maurice Enriquez-Sarano[10]

[1]UR UPJV 7517, Jules Verne University, Amiens, France; [2]University Hospital Amiens, Amiens, France; [3]Fondazione Policlinico Campus Bio-Medico, Università Campus Bio-Medico, Rome, Italy; [4]Cardiology Department, La Timone Hospital, AP–HM, Marseille, France; [5]Pôle de Recherche Cardiovasculaire, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels, Belgium; [6]Department of Cardiovascular Disease, Mayo Clinic, Rochester, MN, USA; [7]Division of Cardiology, Department of Health Sciences, San Paolo Hospital, ASST Santi Paolo e Carlo, University of Milan, Milan, Italy; [8]Division of Cardiology, Department of Diagnostics, Clinical and Public Health Medicine, Policlinico University Hospital of Modena, Modena, Italy; [9]Division of Echocardiography, Cardio X Clinic, Cannes, France; and [10]Department of Cardiovascular Diseases, Minneapolis Heart Institute, Abbott Northwestern Hospital, Minneapolis, MN, USA

Received 19 March 2024; revised 16 June 2024; accepted 8 July 2024

Aims In patients with degenerative mitral regurgitation (DMR), left ventricular (LV) dysfunction is associated with increased risk of heart failure and excess mortality. LV end-systolic diameter (LVESD) is an established trigger for intervention, yet recommended LVESD thresholds apply poorly to patients with small body size. Whether LV normalization to body surface area (BSA) may be used as a trigger for DMR correction is unknown. We examined the link between LVESD index (LVESDi) and outcome in DMR to identify appropriate thresholds for excess mortality.

Methods and results This study focuses on 2753 consecutive patients with DMR due to flail leaflets diagnosed in tertiary centres from Europe and the United States, with prospective echocardiographic measurement of LVESD and BSA and long-term follow-up. The primary endpoint was mortality after diagnosis under conservative management. Secondary endpoints were mortality under conservative and surgical management and postoperative mortality of patients who underwent surgery. The optimal LVESDi cut-off for mortality prediction was 20 mm/m^2. Irrespective of management type, 10-year survival was lower with LVESDi ≥20 mm/m^2 than with LVESDi <20 mm/m^2 (both $p < 0.001$). After covariate adjustment, LVESDi ≥20 mm/m^2 was independently predictive of mortality under conservative management (adjusted hazard ratio [HR] 1.41, 95% confidence interval [CI] 1.15–1.75), and with conservative and surgical management (adjusted HR 1.34, 95% CI 1.17–1.54). LVESDi remained associated with poorer postoperative outcome in patients who underwent intervention. LVESDi showed higher incremental predictive value over the baseline model compared to LVESD. The association between LVESDi ≥20 mm/m^2 and outcome was consistent in subgroups of patients with DMR.

Conclusions In severe DMR due to flail leaflets, LVESDi is a marker of risk additive and incremental to LVESD. Its use in clinical practice should lead to earlier referral to mitral valve surgery and improved long-term outcome.

Keywords Left ventricular dysfunction • Mitral regurgitation • Mortality • Valve intervention

*Corresponding author. UR UPJV 7517, Jules Verne University and University Hospital Amiens, Avenue René Laënnec, 80054 Amiens Cedex 1, France. Tel: +33 3 22455883, Fax: +33 3 22455658, Email: tribouilloy.christophe@chu-amiens.fr

Introduction

In degenerative mitral regurgitation (DMR), left ventricular (LV) enlargement results from chronic volume overload, and is associated with increased risk of heart failure, arrhythmia and mortality. US and European guidelines advocate mitral valve surgery (MVS) in patients with DMR and significant LV enlargement and/or systolic dysfunction. The 40 mm LV end-systolic diameter (LVESD) cut-point is currently a well established trigger for intervention in patients with severe primary mitral regurgitation (MR).[1,2] Because body size influences chamber dimensions, body surface area (BSA) indexation is commonly used to reduce LV dimension variability. Despite this logical approach, previous studies focused essentially on non-indexed LVESD.[3–7] Evidence on the use of LVESD index (LVESDi) in DMR is scarce[7] and current guidelines do not recommend any BSA-indexed LVESD cut-point for the timing of MVS.[1,2]

We aimed to establish the link between LVESDi and outcome in patients with DMR and identify the best cut-off that predicts mortality.

Methods

All participating centres provided institutional review board approval. The study was conducted in accordance with institutional policies, national legal requirements, and the revised Helsinki Declaration. The MIDA registry systematically merged the consecutive experience with DMR by flail leaflets of six tertiary centres: two in France (Amiens, Marseille), two in Italy (Bologna, Modena), one in Belgium (Brussels), and one in the United States (Mayo Clinic, Rochester, MN). The methodology has been previously reported.[7] Briefly, patients were included in the registry between 1980 and 2005 if the following criteria were met: (i) transthoracic echocardiographic diagnosis of DMR by flail leaflets; (ii) comprehensive clinical/instrumental evaluation at baseline echocardiography; (iii) exclusion of ischaemic MR; (iv) absence of moderate/severe aortic valve disease, pericardial/congenital diseases, mitral stenosis, or prior valve surgery; and (v) absence of denial of research authorization. LV dimensions were assessed from parasternal views by M-mode measurements at end-diastole and end-systole or by two-dimensional measurements when M-mode measurements were inadequate.

The primary endpoint was mortality after diagnosis under conservative management. Secondary endpoints were mortality under conservative and surgical management (irrespective of the management received), and postoperative mortality of patients who underwent MVS. For the analysis under conservative management, patients who underwent MVS were censored as non-events at the time of surgery. The study of mortality under conservative and surgical management used the entire follow-up and the total number of events (deaths) and multivariable analyses were systematically adjusted for MVS as a time-dependent covariate. Mean overall follow-up was 8.4 ± 5.1 years and was 98% complete. Events were ascertained by clinical interviews and/or telephone calls to physicians, patients, and (if necessary) next of kin. Medical treatment was left at the discretion of the patients' attending cardiologist and therefore was not standardized. Modifications of pharmacological therapy were not recorded during follow-up. In each centre, MVS was indicated by the attending cardiologist after taking into consideration patient's preference, the opinion of the local heart team and practice guidelines.

Continuous variables were expressed as mean ± 1 standard deviation and compared with Student's *t*-tests. Categorical variables were summarized as frequency percentages and analysed by χ^2 tests. The optimal LVESDi cut-point for survival was established by the maximally selected rank statistics and by inspection of the spline curve graph (maxstat and termplot packages in R, R Foundation, Vienna, Austria). Estimated survival rates ± 1 standard errors were determined using the Kaplan–Meier estimator and compared by two-sided log-rank tests. Mortality analyses were performed using Cox proportional hazards models with LVESDi in continuous and binary form. Comorbidity was assessed by the European System for Cardiac Operative Risk Evaluation (EuroSCORE) II. Multivariable models were adjusted for age, sex, comorbidity and covariates of prognostic impact (symptoms, atrial fibrillation at baseline, coronary artery disease, and MVS). To assess the additive prognostic value of LVESD and LVESDi, we evaluated the ability of each parameter to improve the prediction of death by comparing the additional increase of the χ^2 value of the combined model over the baseline model. For the analysis of outcome under conservative management, patients were censored at the time of MVS if performed. For the analysis of overall survival, MVS was treated as a time-dependent variable. Subgroup analyses were conducted by means of Cox analyses with interaction tests.

Results

The baseline characteristics of the 2753 patients by LVESDi are presented in *Table 1*. The optimal LVESDi cut-off for mortality prediction was 20 mm/m^2 (M statistic 6.07, $p < 0.0001$). This was confirmed by inspection of the spline curve graph (*Figure 1A*). Patients with LVESDi $\geq$20 mm/m^2 tended to be older, less often males, had lower body mass index and BSA, and more severe symptoms than patients with LVESDi <20 mm/m^2. Patients with LVESDi <20 mm/m^2 had less often coronary artery disease and atrial fibrillation, greater LV ejection fraction, less left atrial enlargement, and lower levels of pulmonary pressures (*Table 1*).

Under conservative management, 10-year survival was substantially lower with LVESDi $\geq$20 mm/m^2 than with LVESDi <20 mm/m^2 ($32 \pm 4\%$ vs. $54 \pm 3\%$, $p < 0.001$; *Figure 1B*). After adjustment for age, sex, and comorbidity, LVESDi $\geq$20 mm/m^2 was independently predictive of mortality under conservative management (adjusted hazard ratio [HR] 1.47, 95% confidence interval [CI] 1.19–1.81; $p < 0.001$). Further adjustment for symptoms, atrial fibrillation, and coronary artery disease did not modify the strength of this association (*Table 2*). Similar results were obtained with LVESDi modelled as a continuous variable (*Table 2*). LVESDi showed higher incremental predictive value over the baseline model (including age, sex, EuroSCORE II, symptoms, atrial fibrillation, and coronary artery disease) compared to LVESD (additional value of the χ^2 of the model: 8.59 for LVESDi, $p = 0.003$; 3.21 for LVESD, $p = 0.025$). The mortality effect of LVESDi $\geq$20 mm/m^2 was consistently observed in subgroups of patients with DMR (*Figure 2*). There was no interaction between sex and the outcome impact of LVESDi $\geq$20 mm/m^2 (adjusted *p* for interaction 0.47).

To analyse the outcome of patients according to the LVESD and LVESDi cut-point values, we delineated three subgroups of patients: subgroup 1, LVESD $\geq$40 mm (685 patients); subgroup 2, LVESD <40 mm and LVESDi $\geq$20 mm/m^2 (446 patients); and

Table 1 Baseline characteristics of 2753 patients with degenerative mitral regurgitation due to flail leaflets by left ventricular end-systolic diameter index

Variable	LVESDi <20 mm/m² (*n* = 1719)	LVESDi ≥20 mm/m² (*n* = 1034)	*p*-value
Age, years	65.9 ± 12.9	66.7 ± 13.9	0.13
Body surface area, m²	1.93 ± 0.22	1.80 ± 0.21	<0.001
Body mass index, kg/m²	26.2 ± 4.4	24.1 ± 3.9	<0.001
Male sex, *n* (%)	1314 (76.4)	677 (65.5)	<0.001
NYHA class, *n* (%)			<0.001
I	749 (43.6)	353 (34.1)	
II	592 (34.4)	322 (31.1)	
III	287 (16.7)	263 (25.4)	
IV	91 (5.3)	96 (9.3)	
Coronary artery disease, *n* (%)	258 (15.0)	188 (18.2)	0.029
Hypertension, *n* (%)	701 (40.8)	386 (37.3)	0.07
Diabetes mellitus, *n* (%)	118 (6.9)	81 (7.8)	0.35
Dyslipidaemia, *n* (%)	616 (35.8)	359 (34.7)	0.55
Infective endocarditis, *n* (%)	73 (4.2)	54 (5.2)	0.24
EuroSCORE II, %	1.18 ± 1.05	1.54 ± 1.54	<0.001
Atrial fibrillation, *n* (%)	347 (20.0)	289 (27.9)	<0.001
LV end-diastolic diameter, mm	56.1 ± 6.0	62.0 ± 7.5	<0.001
LVESD, mm	32.7 ± 4.6	41.4 ± 6.8	<0.001
LVESDi, mm	16.9 ± 1.9	23.0 ± 3.1	<0.001
Ejection fraction, %	67.4 ± 7.1	58.6 ± 11.2	<0.001
Left atrial diameter, mm	48.9 ± 7.3	52.1 ± 9.4	<0.001
Systolic pulmonary pressure, mmHg	42.3 ± 16.6	44.2 ± 17.3	0.015
Severe DMR, *n* (%)	1600 (93.1)	978 (94.6)	0.58
ACEI/ARB, *n* (%)	804 (46.8)	455 (44.0)	0.16
Beta-blockers, *n* (%)	535 (31.1)	305 (29.5)	0.39
Diuretics, *n* (%)	650 (37.8)	451 (43.6)	0.002
Oral anticoagulants, *n* (%)	588 (34.2)	359 (34.7)	0.24

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DMR, degenerative mitral regurgitation; EuroSCORE, European System for Cardiac Operative Risk Evaluation; LV, left ventricular; LVESD, left ventricular end-systolic diameter; LVESDi, left ventricular end-systolic diameter index; NYHA, New York Heart Association.

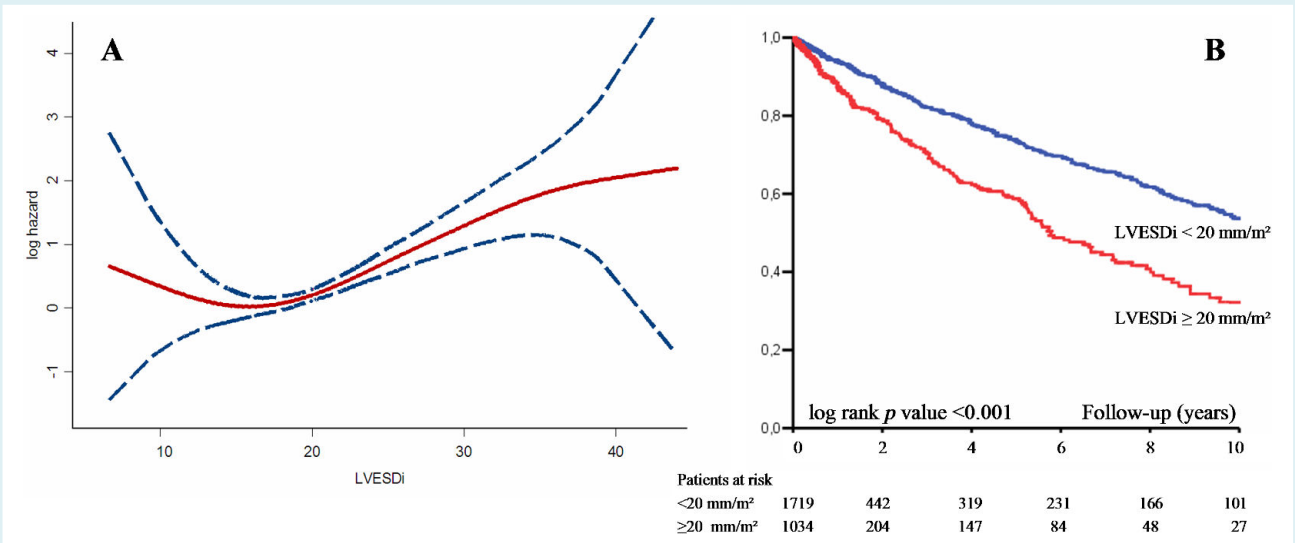

Figure 1 (*A*) Association between left ventricular end-systolic diameter index (LVESDi) and the risk of mortality under conservative management. Hazard ratio (solid line) and 95% confidence intervals were estimated in a Cox multivariable model with left ventricular end-systolic diameter represented as a spline function and adjusted for age, sex, and comorbidity. (*B*) Survival curves by LVESDi under conservative management.

Table 2 Relative risk of death associated with left ventricular end-systolic diameter index in patients with degenerative mitral regurgitation due to flail leaflets – results of Cox analyses

	Conservative management[a]		Conservative and surgical management[b]		Postoperative outcome[a]	
Model	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
LVESDi ≥20 mm/m^2						
Unadjusted	1.84 (1.50–2.25)	<0.001	1.36 (1.19–1.55)	<0.001	1.23 (1.03–1.48)	0.024
Adjusted for age, sex and comorbidity	1.47 (1.19–1.81)	<0.001	1.29 (1.13–1.48)	<0.001	1.21 (1.02–1.45)	0.035
Adjusted for age, sex, comorbidity, symptoms, CAD and AF	1.41 (1.15–1.75)	<0.001	1.34 (1.17–1.54)	<0.001	1.19 (1.01–1.43)	0.048
Per 1-mm increment in LVESDi						
Unadjusted	1.09 (1.06–1.12)	<0.001	1.06 (1.05–1.08)	<0.001	1.06 (1.04–1.08)	<0.001
Adjusted for age, sex and comorbidity	1.06 (1.04–1.09)	<0.001	1.05 (1.03–1.07)	<0.001	1.05 (1.02–1.07)	<0.001
Adjusted for age, sex, comorbidity, symptoms, CAD, and AF	1.05 (1.02–1.07)	0.002	1.04 (1.02–1.06)	<0.001	1.04 (1.01–1.06)	0.002

AF, atrial fibrillation; CAD, coronary artery disease; CI, confidence interval; EuroSCORE, European System for Cardiac Operative Risk Evaluation; HR, hazard ratio; LVESDi, left ventricular end-systolic diameter index.
[a]Analyses of outcome under conservative management and postoperative outcome included age, sex, EuroSCORE II, presence of symptoms at baseline, AF at baseline, and history of CAD as covariates.
[b]Analysis of outcome with conservative and surgical treatment included the above-mentioned covariates and mitral valve surgery as time-dependent covariate.

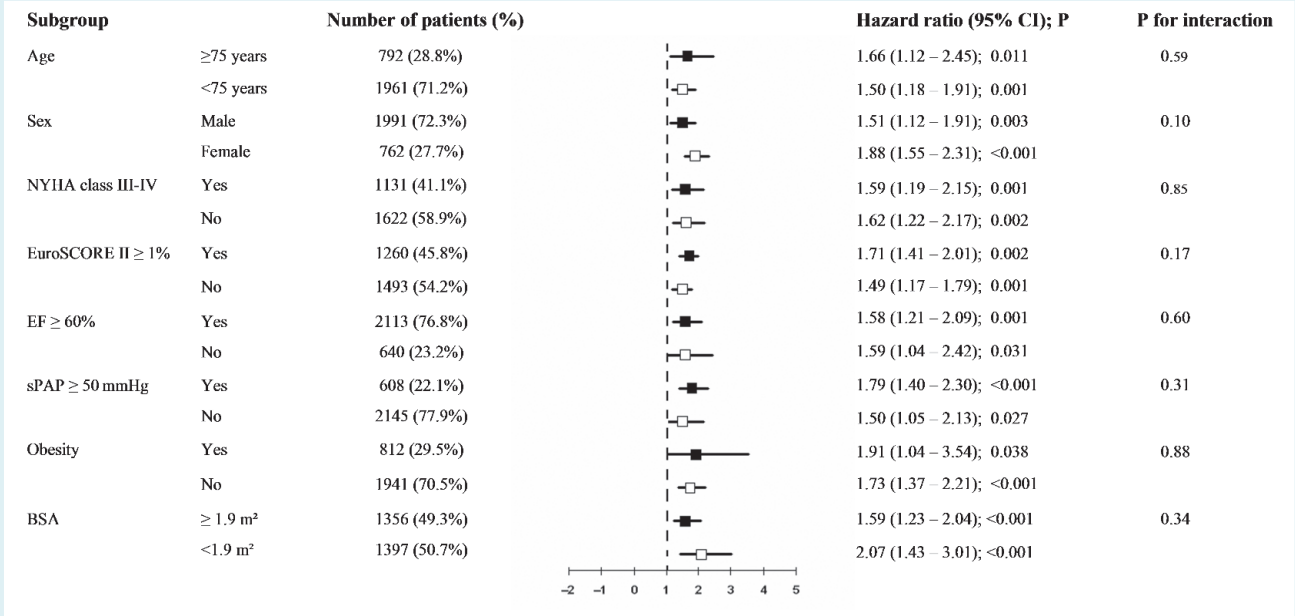

Figure 2 Hazard ratio and 95% confidence interval (CI) for risk of mortality associated with left ventricular end-systolic diameter index ≥20 mm/m^2 in subgroups of patients with degenerative mitral regurgitation. BSA, body surface area; EF, ejection fraction; EuroSCORE, European System for Cardiac Operative Risk Evaluation; NYHA, New York Heart Association; sPAP, systolic pulmonary artery pressure. Obesity is defined as a body mass index ≥30 kg/m^2.

subgroup 3, LVESD <40 mm and LVESDi <20 mm/m^2 (1622 patients). Compared to LVESD ≥40 mm, patients with LVESD <40 mm and LVESDi <20 mm/m^2 were older, had slightly lower BSA, higher prevalence of female sex, less severe symptoms, lower frequency of coronary artery disease and atrial fibrillation, lower EuroSCORE II, lower degree of left atrial enlargement, higher ejection fraction, and lower pulmonary pressure (all $p < 0.05$) Patients with LVESD <40 mm and LVESDi ≥20 mm/m^2 represented approximately 16% of the study population and were older, women in the vast majority, with lower body mass index and BSA, had less left atrial enlargement, and higher ejection fraction than patients with LVESD ≥40 mm (all $p < 0.001$). Under conservative management, patients with LVESD <40 mm and LVESDi ≥20 mm/m^2 had similar 10-year survival compared to patients with LVESD ≥40 mm (34.6 ± 5% and 32.4 ± 5%, respectively; $p = 0.47$). Compared to the two other groups, 10-year survival was significantly higher for patients with LVESD <40 mm and LVESDi <20 mm/m^2 (10-year survival: 53.5 ± 3%, *p*-values for both comparisons < 0.001). Survival under medical management analysis in the three groups is presented in *Figure 3* showing the Kaplan–Meier analysis demonstrating superior survival among patients with neither LVESD ≥40 mm nor LVESDi ≥20 mm/m^2, confirmed in multivariable analysis indicated by the low adjusted HR in this group, while no significant difference was noted between groups with either LVESD ≥40 mm or LVESD <40 mm and LVESDi ≥20 mm.

For the analysis of outcome with conservative and surgical management, 10-year survival was 64 ± 2% with LVESDi ≥20 mm/m^2 and 72 ± 1% with LVESDi <20 mm/m^2 ($p < 0.001$). After covariate adjustment, LVESDi ≥20 mm/m^2 and LVESDi in continuous form independently predicted mortality with conservative and surgical management (*Table 2*). Outcome prediction of LVESDi was not impacted by sex (adjusted *p* for interaction 0.15).

During follow-up, 2169 patients (78.8%) eventually underwent MVS and in 1739 patients (80%) MVS was performed within 6 months after diagnosis. Mitral valve repair was performed in about 90% of patients who underwent intervention ($p = 0.77$ for LVESDi <20 mm/m^2 vs. ≥20 mm/m^2). MVS analysed as a time-dependent covariate was associated with marked mortality reduction during follow-up (adjusted HR 0.34, 95% CI 0.28–0.42, $p < 0.001$). The beneficial effect of surgery was of comparable magnitude in patients with LVESDi <20 mm/m^2 and in patients with LVESDi ≥20 mm/m^2 (adjusted *p* for interaction 0.30). For post-surgical outcome, LVESDi ≥20 mm/m^2 remained predictive of postoperative mortality (adjusted HR 1.19, 95% CI 1.01–1.43, $p = 0.048$; *Table 2*). LVESDi ≥20 mm/m^2 impacted postoperative outcome similarly in both sexes (adjusted *p* for interaction 0.13). Patients with LVESDi ≥20 mm/m^2 who underwent MVS within 6 months after diagnosis exhibited better long-term outcome compared to those in whom MVS was subsequently performed (adjusted HR 1.46, 95% CI 1.04–2.03, $p = 0.027$).

Discussion

Degenerative MR benefits from wide applicability of valve repair, surgical mostly, but also transcatheter for high-risk patients,[1] but unfortunately remains profoundly undertreated. Medical therapies for severe chronic DMR have shown inconsistent results. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and beta-blockers are not recommended for the prevention of LV dysfunction or to delay surgery in chronic severe DMR with normal blood pressure. In such patients, pharmacological

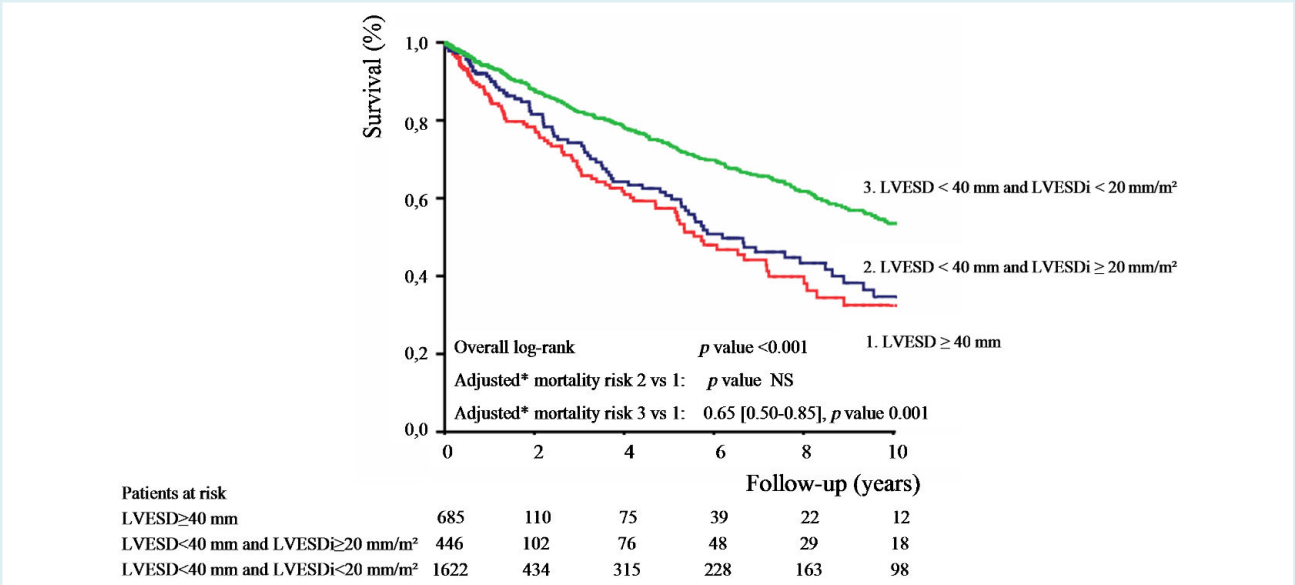

Figure 3 Survival curves of patients stratified by left ventricular end-systolic diameter (LVESD) and LVESD index (LVESDi) cut-point values (40 mm and 20 mm/m^2) under conservative management. EuroSCORE II, European System for Cardiac Operative Risk Evaluation. *Adjustment for age, sex, EuroSCORE II, presence of symptoms at baseline, atrial fibrillation at baseline, and history of coronary artery disease.

therapy may obscure symptoms and lead to missed opportunities of timely valve surgery. Conversely, patients with severe DMR presenting with overt LV systolic dysfunction and/or symptoms of heart failure require pharmacological treatment as per guidelines and prompt rescue mitral surgery. Nevertheless, patients with severe DMR who undergo valve surgery according to LV function class I recommendations (ejection fraction <50%) incur unacceptable risk of postoperative LV dysfunction, heart failure and reduced life expectancy compared to the general population. The ongoing search of markers and thresholds of risk under conservative management is therefore directed to optimize timing of intervention and improve postoperative outcomes. Whether medical therapy after mitral valve repair improves the outcome of patients with overt LV dysfunction has not yet been tested in a clinical trial and remains a relevant question.

Clinical guidelines provide as a class I trigger for surgery the LV end-systolic dimension[1] which reflects its fundamental link to myocardial contractility and to long-term DMR prognosis.[3–7] However, absolute LVESD use may cause bias directed to patients with low body size, particularly women.[8] Clinical guidelines have incorporated LVESD indexed to BSA for aortic regurgitation as it has long been demonstrated to be associated with outcome. LVESDi >25 mm/m^2 is therefore an established trigger for intervention in patients with aortic regurgitation. Conversely, absent proof that in patients with DMR, LVESDi is associated with outcome, prevented its incorporation in clinical guideline triggers for DMR correction.

The present effort addresses this gap of evidence. Indeed, the 20 mm/m^2 LVESDi cut-point shows good outcome predictive ability and better prognostic performance compared to LVESD. LVESDi may be especially interesting in women and in patients with small body size who display less absolute cardiac chamber enlargement despite considerable volume overload. LVESDi allows further stratification of patients with LVESD <40 mm into a high risk group (LVESDi ≥20 mm/m^2) with outcome similar to that of LVESD ≥40 mm and a group with lower risk (LVESDi <20 mm/m^2). Patients who experience progressive chamber dilatation with LVESDi reaching 20 mm/m^2 should be referred to early surgery to improve overall prognosis. The results of this study documenting the link between LVESDi and long-term outcome support its use for risk prediction and for timing of DMR surgical or interventional correction.

While in the present study clinical and non-echocardiographic data were obtained by retrospective review of medical records, echocardiographic data were prospectively collected, which should reassure about potential biases. Also, this study is not a clinical trial, as clinical consecutive cohorts are best suited to define long-term outcome under medical management and are similar in design to all studies that led to inclusion of class I triggers for DMR correction[1] This study used 'flail leaflet' as a surrogate for severe MR. According to guidelines,[9–11] the presence of a "flail leaflet" is a specific sign of severe MR. Although prominent flail usually is associated with severe MR, not all flail leaflets are associated with severe MR, and not all patients in this study were felt, at the time of echocardiography interpretation, to have severe MR. Indeed, in our study, 94% of patients were classified as severe MR (grade 4) and 6% as moderate-to-severe MR (grade 3), using an integrative echocardiographic evaluation. Moreover, the final grading of DMR does not impact the results of our study, as LVESDi ≥20 mm/m^2 affects similarly survival under conservative management in those graded as severe MR (5-year survival: 58 ± 3% vs. 72 ± 2%, $p < 0.001$) and in those graded less than severe (5-year survival: 63 ± 12% vs. 81 ± 5%, $p = 0.02$). Thus, we do not believe that our use of flail leaflet as a surrogate for severe DMR represents a bias versus guidelines or versus the hypothesis examined in the present study. Although surgical methods to repair the mitral valve have evolved during the study period, all studies consistently show superiority of valve repair over replacement.[12]

Conclusion

In patients with severe DMR by flail mitral valve leaflets, the 20 mm/m^2 LVESDi cut-point is a marker of risk additive and incremental to LVESD and demonstrates significant and independent outcome prediction after diagnosis. Its use in clinical practice should lead to earlier referral to MVS and improved long-term outcome.

Conflict of interest: none declared.

References

1. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F, *et al.* 2020 ACC/AHA Guideline for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2021;**143**:e72–e227. https://doi.org/10.1161/CIR.0000000000000923
2. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, *et al.*; ESC/EACTS Scientific Document Group. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2021;**43**:561–632. https://doi.org/10.1093/eurheartj/ehab395
3. Enriquez-Sarano M, Tajik AJ, Schaff HV, Orszulak TA, McGoon MD, Bailey KR, *et al.* Echocardiographic prediction of left ventricular function after correction of mitral regurgitation: Results and clinical implications. *J Am Coll Cardiol* 1994;**24**:1544–1546. https://doi.org/10.1016/0735-1097(94)90151-1
4. Matsumura T, Ohtaki E, Tanaka K, Misu K, Tobaru T, Asano R, *et al.* Echocardiographic prediction of left ventricular dysfunction after mitral valve repair for mitral regurgitation as an indicator to decide the optimal timing of repair. *J Am Coll Cardiol* 2003;**42**:458–463. https://doi.org/10.1016/S0735-1097(03)00649-1
5. Wisenbaugh T, Skudicky D, Sareli P. Prediction of outcome after valve replacement for rheumatic mitral regurgitation in the era of chordal preservation. *Circulation* 1994;**89**:191–197. https://doi.org/10.1161/01.cir.89.1.191
6. Suri RM, Schaff HV, Dearani JA, Sundt TM, Daly RC, Mullany CJ, *et al.* Recovery of left ventricular function after surgical correction of mitral regurgitation caused by leaflet prolapse. *J Thorac Cardiovasc Surg* 2009;**137**:1071–1076. https://doi.org/10.1016/j.jtcvs.2008.10.026
7. Tribouilloy C, Grigioni F, Avierinos JF, Barbieri A, Rusinaru D, Szymanski C, *et al.*; MIDA Investigators. Survival implication of left ventricular end-systolic diameter in mitral regurgitation due to flail leaflets: A long-term follow-up multicenter study. *J Am Coll Cardiol* 2009;**54**:1961–1968. https://doi.org/10.1016/j.jacc.2009.06.047
8. Mantovani F, Clavel MA, Michelena HI, Suri RM, Schaff HV, Enriquez-Sarano M. Comprehensive imaging in women with organic mitral regurgitation: Implications for clinical outcome. *JACC Cardiovasc Imaging* 2016;**9**:388–396. https://doi.org/10.1016/j.jcmg.2016.02.017
9. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, *et al.* Recommendations for noninvasive evaluation of native valvular regurgitation: A report from the American Society of Echocardiography. Developed in collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr* 2017;**30**:303–371. https://doi.org/10.1016/j.echo.2017.01.007
10. Lancellotti P, Moura L, Pierard LA, Agricola E, Popescu BA, Tribouilloy C, *et al.*; European Association of Echocardiography. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: Mitral and tricuspid regurgitation (native valve disease). *Eur J Echocardiogr* 2010;**11**:307–332. https://doi.org/10.1093/ejechocard/jeq031

11. Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, *et al.*; American Society of Echocardiography. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 2003;**16**:777–802. https://doi.org/10.1016/S0894-7317(03)00335-3

12. Lazam S, Vanoverschelde JL, Tribouilloy C, Grigioni F, Suri RM, Avierinos JF, *et al.*; MIDA (Mitral Regurgitation International Database) Investigators. Twenty-year outcome after mitral repair versus replacement for severe degenerative mitral regurgitation: Analysis of a large, prospective, multicenter, international registry. *Circulation* 2017;**135**:410–422. https://doi.org/10.1161/CIRCULATIONAHA.116.023340