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ORIGINAL RESEARCH

Disproportionate Left Ventricular Enlargement in Mitral Valve Prolapse: Prevalence, Predictors, and Association With Outcomes

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BACKGROUND: Left ventricular (LV) end-systolic enlargement in severe degenerative mitral-regurgitation (MR) is a class I surgical trigger. Whether it occurs disproportionately to less-than-severe MR due to mitral valve prolapse and is associated with mortality are unknown. We aimed to analyze prevalence and association with survival of disproportionate LV enlargement in less-than-severe MR.

METHODS: A multicenter cohort international study enrolled 2848 consecutive patients (52% women, 69±16 years) with degenerative MR prospectively quantified and graded mild or moderate. Primary end point was survival under medical management. Secondary outcome was survival throughout follow-up stratified by performance of early mitral surgery within 3 months postdiagnosis.

RESULTS: Among LV remodeling parameters (abnormal end-diastolic diameter, LV end-systolic diameter [LVESD] absolute and indexed), LVESD ≥40 mm (present in 12.4%) was the sole independent associate of reduced survival (5-year 70±3 versus 76±9%; *P*=0.009). LVESD ≥40 mm was independently linked to larger body surface area, effective regurgitant orifice, and left atrium, and to male sex and diabetes. With multivariable comprehensive adjustment, LVESD ≥40 mm (adjusted hazard ratio [aHR], 1.25 [95% CI, 1.005–1.53]; *P*=0.04) remained associated with excess mortality under medical management, even after adjustment for lowered ejection fraction (aHR, 1.49 [95% CI, 1.13–1.95]; *P*=0.004) and in all patient subsets. Among patients with moderate degenerative MR and LVESD ≥40 mm, 22% underwent mitral surgery within 3 months, which was associated with superior survival, even after comprehensive adjustment (aHR, 0.11 [95% CI, 0.005–0.51]; *P*=0.002).

CONCLUSIONS: Disproportionate LV enlargement in patients with less-than-severe degenerative MR is common, particularly with larger bodies, regurgitation, and overall cardiac remodeling. LVESD ≥40 mm is associated with worse survival independent of all baseline characteristics, even lowered ejection fraction, and represents a marker for risk stratification of patients who are generally not yet considered for medical or surgical/interventional treatment.

Key Words: degenerative mitral regurgitation ■ left ventricular ■ mitral valve prolapse

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CLINICAL PERSPECTIVES

What Is New?

- In patients with less-than-severe mitral-regurgitation, the best disproportionate left ventricular (LV) enlargement predictor of survival is end-systolic diameter ≥40 mm.
- The prevalence of end systolic diameter ≥40 mm in patients with less-than-severe mitral regurgitation is ≈12%.
- Among patients with mitral valve prolapse, moderate mitral regurgitation, and end-systolic diameter ≥40 mm, early surgery was associated with better survival.

What Are the Clinical Implications?

- Our study highlights that LV enlargement disproportionate to less-than-severe mitral regurgitation in patients with mitral valve prolapse is relatively common and associated with worse survival. The clinical observation that patients with moderate mitral regurgitation with mitral valve prolapse and disproportionate LV remodeling who are promptly referred to surgery, have superior outcomes over patients who are treated medically, underscores the need for stringent LV volumetric assessment, possibly by cardiac magnetic resonance imaging, and for the considering mitral surgery in the patients with confirmed disproportionate LV remodeling. Future randomized controlled trials are needed to further evaluate the benefit of earlier intervention. Nevertheless, disproportionate LV remodeling represents an important risk marker to consider in patients for whom mitral regurgitation correction is not yet recommended in clinical guidelines.

Nonstandard Abbreviations and Acronyms

ERO	effective regurgitant orifice
MR	mitral regurgitation

Mitral valve prolapse (MVP) affects approximately 6 million people in the United States.[1,2] Severe mitral regurgitation (MR) due to MVP, also called degenerative MR (DMR), is associated with increased morbidity and mortality[3] and can often be treated with surgery with major indications based on left ventricular (LV) consequences.[4,5] These LV consequences are difficult to assess in DMR because increased preload and systolic unloading into the left atrium (LA) tend to create the appearance of "normal" contraction and acceptable ejection fraction (EF) although impaired myocardial function may already be present.[6] Conversely, with DMR, there is an obligatory LV dilatation determined by the regurgitant volume, demonstrated with angiography[7] and echocardiography.[8] Experimental and clinical evidence suggests that end-systolic (ES) fiber length, measured clinically by ES volume/diameter (ESD), is the fundamental indicator of ventricular contractile function.[9–11] Indeed, LVESD is linearly related to ES pressure and relatively unaffected by initial preload.[9] The changes in ES pressure–volume relationship reflect the inotropic myocardial state.[12,13] Therefore, the end-systolic LV characteristics are the "primum movens" of all myocardial function measures, but LVESD, as a response to DMR, varies markedly between patients.[7,8] In severe DMR, excessive LV remodeling with large LVESD is independently associated with subsequent LV dysfunction and excess mortality,[14–17] leading to inclusion of excess LVESD remodeling as class I indication for repair of severe DMR.[4,5]

However, little is known about LV remodeling in less-than-severe DMR. Although pilot reports suggested possible disproportionate LV enlargement relative to DMR severity in MVP,[18–20] the prevalence of precisely defined excess LV remodeling in a large cohort of MVP with prospectively quantified DMR and the factors that may be linked to such remodeling are unknown. Furthermore, whether this abnormal response to DMR may affect clinical outcomes remains uncertain and unaddressed in current guidelines.[4,5] The rationale for such analysis is strongly supported by genetic studies, which identified MVP genes straddling those linked to cardiomyopathy.[21] Also, cardiac magnetic resonance imaging[20,22–24] reported myocardial remodeling and fibrosis in MVP with less-than-severe DMR. Another MVP conundrum is the recent demonstration that risks are not confined to severe DMR,[25] with excess mortality emerging in moderate DMR.[20,24–26] Whether such excess mortality is linked to disproportionate LV remodeling is unknown. Therefore, these data warrant examination in a large registry of patients with MVP and quantified DMR, to assess the reality of disproportionate-LV-remodeling in less-than-severe DMR and its implications. The MIDA-Q (Mitral Regurgitation International Database Quantitative) shared data repository enrolled patients with MVP and various degrees of MR prospectively quantified at diagnosis from various countries/continents, providing a unique opportunity to fill these gaps of knowledge. We gathered patients with DMR graded "less than severe" with uniform regurgitation quantitation in routine practice and aimed at defining presence, prevalence, and context of disproportionate LV enlargement and at defining the impact on outcomes.

METHODS

The report follows the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for cohort studies. The data that support the findings of this study are available from the corresponding author upon reasonable request. This DMR cohort study data repository combines consecutive adult patients with isolated MVP in whom DMR was prospectively quantified at diagnosis, from North America (Mayo Clinic, Rochester, MN), Europe (Leiden University, the Netherlands; Amiens University, France; Nantes University, France), and the Middle East (Tel Aviv Medical Center, Israel).[27] Enrollment extended from January 2003 to January 2020. Patients were characterized by (1) MVP diagnosed with MR graded mild or moderate[28]; (2) comprehensive clinical evaluation recorded prospectively at index echocardiography; and (3) LV dimensions measurable at MVP diagnosis. Patients with functional MR, ≥moderate concomitant aortic valve disease, mitral stenosis, congenital heart disease, active endocarditis, and prior valve surgery were excluded. Patients with MVP and DMR graded severe were also excluded. Nevertheless, patients with other systemic comorbidities were not excluded. The study was approved by institutional review boards of each center, conducted in accordance with institutional guidelines, national legal requirements, and the Declaration of Helsinki. Informed consent was waived due to the retrospective nature of analysis of outcome.

Echocardiography

LVEF, LVESD, and LV end-diastolic diameters (LVEDD) were measured per guideline recommendations, and diameters were used as absolute values and indexed for body surface area.[29] LA volume index was calculated from apical 2- and 4-chamber views.[29] MR assessment was based on existing guidelines with, in all patients, collection of all signs and measures as well as MR quantitative measures with final integrative grading using all supportive, specific, and quantitative signs/measures.[28] As recommended, patients with the upper range of moderate MR (moderate to severe) were included as part of the broad moderate MR category.[4,28]

Outcome

Each center was responsible for the completeness of follow-up conducted locally, and overall 90.4% were followed until death or at least 5 years postdiagnosis, 84% were followed until death or at least 8 years postdiagnosis, or the full follow-up available for those diagnosed most recently. Mortality during follow-up was the clinical outcome end point to the study and was collected using direct patient/family/physician contact and using institutional, private (Accurint in the United States), or public (social security mortality database or local equivalent) database. Surgical procedures were collected and dated using institutional surgical registries but also clinical notes or questionnaires for a few patients operated outside their respective institutions. Survival under medical management started at DMR diagnosis by echocardiography in each institution and ends at death, or last follow-up if unoperated. If surgery was performed it was treated as a censoring event. Overall survival started at DMR diagnosis in each institution and ended at death or last follow-up, including postoperative. Postoperative survival started at surgery (unknown in unoperated patients) and ended at death or last follow-up. Symptoms were defined as shortness of breath with rest, less than ordinary, or ordinary physical activity (New York Heart Association Class IV, III, and II). Outcomes were ascertained by investigators blinded to baseline characteristics.

Statistical Analysis

Categorical variables are expressed as numbers and percentages, and continuous variables are presented as mean±SD or median (interquartile range). The main variable of interest was the LVESD ≥40 mm.[4,5] Other measures of disproportionate LV enlargement were abnormal LVEDD index defined per guidelines-nomograms[29] and abnormal LVESD index ≥21 mm/m^2 as per previous cohorts.[17] Associations of LVESD ≥40 mm with clinical/echocardiographic manifestations were analyzed by binary logistic regression models with clinical/echocardiographic manifestations as independent variables and LVESD ≥40 mm as dependent variable. Cox proportional hazards models evaluated survival under medical management, and death was studied separately as end point univariably and adjusted for age, sex, EuroScore II, symptoms (core model), and comprehensively for additional prognostic markers (comprehensive model) with adjusted hazard ratios (HR). Survival was estimated using Kaplan–Meier method and compared using log-rank test. To analyze potential impact of early surgery (<3 months after diagnosis) in patients with moderate DMR on outcomes, a landmark analysis adjusting for core/comprehensive models was performed. In the landmark analysis, time zero was set at 3 months post diagnosis for all patients alive at that point (excluding 19 patients who died within 3 months under medical management to avoid survival bias), with treatment groups defined as early surgery (≤3 months) versus initial medical management, ensuring that early mortality does not bias the comparison. To further account for potential "immortal time bias" among operated patients,[30] analysis of surgery as a time-dependent covariate in a Cox model analyzing all deaths throughout follow-up after diagnosis, using 3 months as time zero. All tests were 2

sided, and a *P* value <0.05 was considered statistically significant. Data were analyzed with the JMP software version 14.0 (SAS Institute, Inc, Cary, NC) and SPSS (IBM Corp., version 28, Armonk, NY).

RESULTS

Baseline Characteristics

The entire cohort included 2848 patients (52% women, age 69±16 years). Baseline demographic/clinical characteristics (Table 1) are typical for MVP with less-than-severe MR, with bileaflet prolapse in 48%, posterior leaflet prolapse in 36%, anterior leaflet prolapse in 16%, and rare flail leaflets in 6%. Clinically, 33% had dyspnea, 43% hypertension, 22% atrial fibrillation, 22% coronary artery disease, and 5% significant hypertrophy, and the EuroScoreII was 1.82±1.86%. MR was mild in 35.5% and moderate in 64.5% (effective regurgitant orifice [ERO] 19±11 mm^2; regurgitant volume 32±15 mL).

Despite the modest volume overload, the enrolled patients displayed relatively frequent disproportionate LV remodeling with enlarged LV defined per guidelines-nomograms noted in 21% based on LVEDD (>58.4 mm in men, >52.2 mm in women), 17% based on LVEDD index (≥31 mm/m^2 in men, ≥32 mm/m^2 in women), 16% based on LVESD (>39.8 mm in men, >34.8 in women),[29] and 13% based on LVESD index (>21 mm/m^2).[17] Finally, using the DMR-guideline-based threshold of LVESD ≥40 mm, 354 (12.4%) were classified as disproportionate LV remodeling, which was retained as the main variable to stratify our cohort. Of those with LVESD ≥40 mm, 132 patients had mild MR and 222 moderate MR.

Baseline demographic/clinical characteristics stratified by LVESD <40 mm versus ≥40 mm are shown Table 1. LVESD ≥40 mm was associated with larger bodies, even when stratified by sex (Table S1). There was no association of disproportionate LV-remodeling with cardiovascular comorbidities, and medical treatment received were similar apart from vasoactive drugs. Conversely, an association was found between disproportionate LV remodeling and atrial fibrillation and diabetes. Regarding mitral characteristics, in the entire cohort, disproportionate LV remodeling was not associated with prolapse type but with slightly larger ERO and regurgitant volume. Interestingly, larger LV was associated with larger LA but no detectable alteration of LV filling, pulmonary pressure, or prevalence of right ventricular dysfunction. Baseline characteristics stratified to North America, Europe, and the Middle East are shown in Table S2.

In terms of possible baseline determinants of disproportionate LV enlargement, multivariable analysis is shown Table 2. Characteristics noted in univariate analysis were confirmed in multivariable analysis, apart from a borderline effect of atrial fibrillation. Larger LA volume index, larger ERO, and larger body surface area, similarly to male sex, were also associated independently with higher odds of disproportionate LV remodeling. Mild MR has a different implication as opposed to moderate, thus baseline characteristics associated with disproportionate LV enlargement in multivariable analysis stratified by mild or moderate DMR and analyses for interaction with severity of MR are shown in Table S3. Most determinants of LVESD ≥40 mm show no interaction by DMR grade, whereas there is a small but significant interaction of sex and DMR grade on LVESD ≥40 mm due to the fact that in men, the proportion of patients with LVESD ≥40 mm decreases slightly in moderate versus mild DMR, possibly related to a lower rate of diabetes in moderate versus mild DMR.

Using LVESD index ≥21 mm/m^2 as alternate marker of disproportionate LV remodeling, the relation with sex became insignificant but diabetes, larger LA volume index, and ERO remained independently related (Table S4).

Identical systolic/diastolic blood pressures in both groups strongly suggest patients with LVESD ≥40 mm had lower LV elastance, that is, a reduction of the fundamental measure of LV contractility,[9–11] including in primary MR.[31] Thus, other LV characteristics are consequential to ES LV alterations. Hence, adjusting for age, sex, cardiac rhythm, ERO, and body surface area, LVESD ≥40 mm was associated with disproportionate LV end-diastolic enlargement (adjusted odds ratio [aOR], 22.6 [95% CI, 11.4–44.9], *P*<0.0001), with worse systolic ejection characteristics (aOR of EF<60%, 9.2 [95% CI, 6.8–12.3], *P*<0.0001) and with more frequent symptoms (aOR of dyspnea symptoms, 1.49 [95% CI, 1.15–1.93], *P*=0.003). Thus, multiple DMR characteristics follow the ES LV alterations, carefully accounted for in analyzing the impact on outcome of disproportionate LV remodeling.

Impact of Disproportionate LV Remodeling on Survival Under Medical Management

Over a median follow-up duration of 4.7 (range, 2.2–7.5) years, 851 patients (29.8%) died under medical management. In adjusted models, LVEDD, LVEDD above the limits of normal, and LVEDD index showed no significant association with survival (all *P*>0.20). We also explored the most appropriate LVESD format, absolute >40 mm, abnormal for each individual based on normalcy defined by guidelines, and indexed LVESD to body surface area. Although each variable was univariately associated with outcome, with any adjustment, the link to outcome of abnormal or indexed LVESD

Table 1. Baseline Clinical and Echocardiographic Characteristics Overall and Stratified by LVESD ≥40 or <40 mm

	Overall population N=2848	ESD<40 mm N=2494	ESD≥40 mm N=354	*P* value
Clinical characteristics				
Age, y	69±16	69±16	68±16	0.10
Female sex, %	52	55	27	<0.0001
Body mass index, kg/m^2	25±4.6	24.9±5	25.8±5	0.0008
Body surface area, m^2	1.80±0.2	1.78±0.2	1.90±0.2	<0.0001
Heart rate, bpm	71±15	71±15	70±15	0.17
Systolic BP, mm Hg	124±18	124±18	124±19	0.75
Diastolic BP, mm Hg	71±11	71±10	70±12	0.30
Atrial fibrillation, %	22	21	27	0.005
Previous coronary artery bypass graft, %	2	2	3	0.23
Coronary artery disease, %	22	21	26	0.12
Hypertension, %	43	44	40	0.42
Diabetes, %	15	14	22	0.0002
Dyspnea, %	33	32	41	0.001
Creatinine clearance, mL/min	58.4±33	62.7±39	54.1±32	0.01
EuroScore II, %	1.82±1.86	1.80±1.86	1.97±1.85	0.10
Vasodilators, %	10.7	9.5	13.1	0.04
Diuretics, %	11.1	11.5	8.7	0.26
Digoxin, %	2.8	2.8	3.1	0.76
Mitral valve surgery, n (%)	527 (19)	441 (18)	86 (24)	0.003
LV and mitral characteristics				
LVEDD, mm	51±6	49±6	59±5	<0.0001
Indexed LVEDD, mm/m^2	28.3±4	27.9±4	31.4±4	<0.0001
Abnormal LVEDD index, %	17.0	13.1	45.7	<0.0001
LVESD, mm	33±6	31±4	44±4	<0.0001
Indexed LVESD, mm/m^2	18.2±3	17.5±3	23.3±3	<0.0001
Abnormal LVESD index, %	12.8	6.1	61.0	<0.0001
LVEF, %	60±8	61±7	51±10	<0.0001
EF <60%, %	32.7	26.9	75.9	<0.0001
EF% <50%, %	9.8	5.5	42.3	<0.0001
LA volume index, mL/m^2	49±19	48±19	55±21	<0.0001
LA diameter, mm	44±8	43±8	46±6	<0.0001
Systolic pulmonary artery pressure, mm Hg	39±14	38±14	39±14	0.26
Mitral characteristics				
Effective regurgitant orifice, mm^2	19±11	19±11	21±12	0.045
Regurgitant volume, mL	32±15	31±15	34±15	0.026
Flail leaflet, %	6	5.5	8.8	0.023
Bileaflet, %	48	49	45	0.53
Anterior, %	16	15	17	0.69
Posterior, %	36	36	38	0.53

BP indicates blood pressure; EDD, end-diastolic diameter; EF, ejection fraction; ESD, end-systolic diameter; LA, left atrium; and LV, left ventricular.

became promptly insignificant, although remaining directionally similar to that of LVESD ≥40 (Tables S5 and S6). Therefore, in examining measures of disproportionate LV remodeling linked to outcome, we retained only LVESD ≥40 mm. Cox proportional hazards models analyzing survival under medical management in regard to LVESD ≥40 mm are summarized in Table 3 and Table S5. Cox proportional hazards models analyzing death studied separately in regard to LVESD ≥40 mm are summarized in Table S7. The HR for LVESD ≥40 mm was almost unaffected by adjustments. Even comprehensive adjustment for LVEF yielded an HR of 1.49 (95% CI, 1.13–1.95; *P*=0.004) for LVESD ≥40 mm. Direct survival comparison according to presence/absence of

Table 2. Multivariable Determinants of Disproportionate LV Remodeling (LVESD ≥40 mm) in Less-Than-Severe DMR

Variable	Threshold	Odds ratio	95% CI	*P* value
Sex	Male	2.66	1.94–3.65	<0.0001
Rhythm	Atrial fibrillation	1.29	0.95–1.75	0.10
Diabetes	Present	1.98	1.44–2.72	<0.0001
Body surface area	≥1.9 m^2	1.71	1.27–2.28	0.0003
Left atrial volume index	≥60 mL/m^2	1.87	1.38–2.53	0.0001
Effective regurgitant orifice	≥0.30 cm^2	1.42	1.03–1.95	0.03

DMR indicates degenerative mitral regurgitation; LV, left ventricular; and LVESD, LV end-systolic diameter. Area under the curve=0.725.

disproportionate LV remodeling is shown in Figure 1 demonstrating the significant impact of LVESD ≥40 mm on survival under medical management. Mild MR may have a different implication as opposed to moderate, thus we analyzed the interaction of survival under medical management in regard to LVESD ≥40 mm stratified for mild or moderate MR (Table 3). With all possible adjustments, there is no significant interaction between the effect of LVESD ≥40 mm on survival under medical management and the DMR grade.

Subgroup Analyses

The impact of disproportionate LV remodeling on survival under medical management was assessed in adjusted analyses in various subgroups (Figure 2). It was associated with excess mortality in older (≥75 years, *P*=0.002) or <75 years (*P*=0.009), EuroScore II ≥1% (*P*<0.0001) or <1% (*P*=0.09), moderate (*P*<0.0001) or mild DMR (*P*=0.02), and with (*P*=0.03) or without diabetes (*P*=0.002). No significant interactions were noted for all subgroups (all *P*>0.40).

Table 3. Cox Proportional Hazards Analyses for Association of LVESD ≥40 mm and Mortality Under Medical Management

	Hazard ratio	95% CI	*P* value	*P* interaction LVESD-DMR grade
Univariable analysis	1.29	1.06–1.55	0.01	0.90
Adjustment*	1.38	1.13–1.68	0.002	0.51
Adjustment†	1.25	1.005–1.53	0.04	0.44
Comprehensive adjustment‡	1.27	1.02–1.57	0.03	0.45
Comprehensive echo adjustment§	1.65	1.27–2.11	0.0001	0.47
Comprehensive echo adjustment with EF¶	1.49	1.13–1.95	0.004	0.25

DMR indicates degenerative mitral regurgitation; EDD; end-diastolic diameter; EF, ejection fraction; ERO, effective regurgitant orifice; ESD, end-systolic diameter; and LV, left ventricular.

*Age, sex, EuroScore II.

†Age, sex, atrial fibrillation, dyspnea, EuroScore II.

‡Age, sex, symptoms, atrial fibrillation, ERO, and EuroScore II.

§Adjustment for age, sex, symptoms, LVEDD, ERO, and EuroScor II.

¶Adjustment for age, sex, symptoms, LVEDD, ERO, EF<60, and EuroScore II.

Clinical Management and Surgery

Clinical management was ultimately medical in 2321 patients (81%) and medical followed by mitral surgery in 527 (19%) patients. DMR surgery was valve repair in 467 (89%), replacement in 58 (11%), and unclassified in 2. Mitral surgery was more common in patients with disproportionally enlarged LV than in those without (25±3% 5-year post diagnosis versus 19±1%, *P*=0.0002), particularly with moderate DMR (36±4% versus 26±1%, *P*<0.0001). We analyzed the determinants of proceeding with surgery at any time in the entire cohort. The determinants of the surgical indication were logical and related to more MR, more consequences, and lower risk in performing mitral surgery (Table S8).

Among the patients graded with mild MR, only 29 (2.9%) ultimately underwent mitral surgery, an average of 1.6 years after the initial diagnosis, whereas among the patients diagnosed with moderate DMR, 498 (27%) ultimately underwent mitral surgery an average of 1.4 years after diagnosis. We selected 3 months as the window for performance of early surgical intervention based on the clinical observation of the practicalities of patients making arrangements to schedule and undergo mitral valve surgery and on the distributions of time to surgery within the first year postdiagnosis. Among patients with moderate DMR and disproportionate LV remodeling, 49 (22%) underwent mitral surgery (<3 months post diagnosis). Only 11.8% (32/173) of the patients with moderate DMR, disproportionate LV remodeling, and initial medical management subsequently underwent mitral surgery. Baseline demographic/clinical characteristics of the patients with moderate DMR and disproportionate LV remodeling stratified by mitral early surgery (<3 months post diagnosis) are shown Table S9. In 7 (14%) and 5 (10%) patients, the surgery was performed in combination with coronary artery bypass graft/aortic and tricuspid surgery, respectively. In the others, there was no other intervention planned during the surgery and symptoms were quite frequent (59%). In all patients the decision to proceed with surgery was at the discretion of the personal cardiologist with the patients. Early surgery in moderate DMR was associated with higher survival in univariable analysis (HR, 0.46 [95% CI, 0.38–0.55]; *P*<0.0001, Figure 3), and adjusted for age, sex, dyspnea, atrial fibrillation, ERO, LVEF, and EuroScore II (adjusted HR, 0.48 [95% CI, 0.30–0.73], *P*=0.0006). Early surgery was associated with more impressive mortality

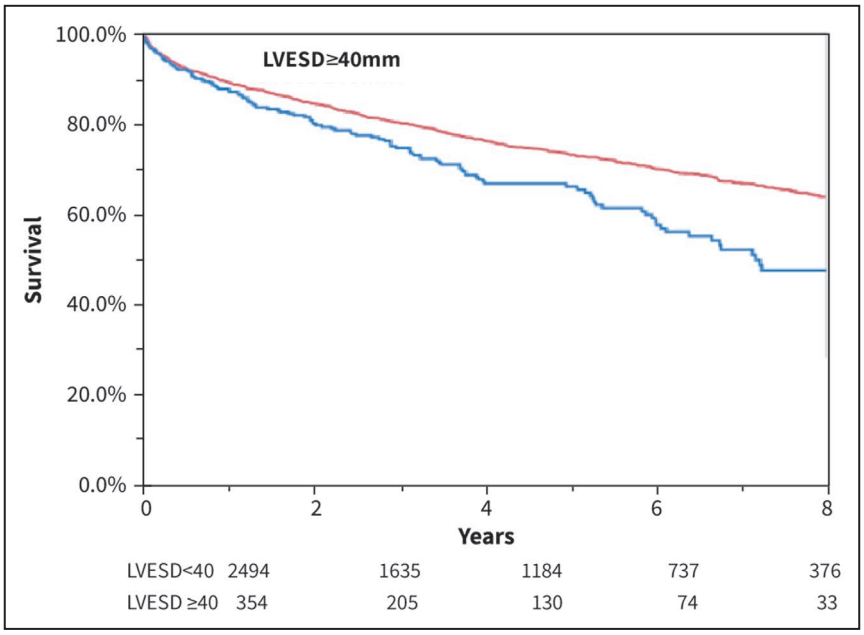

Figure 1. Survival stratified by LV size parameters.
Kaplan–Meier curves for LV size parameters followed under medical management. (LVESD ≥40 mm blue line, <40 mm red line). Note the marked separation between curves maintained throughout the entire follow-up period in the LV end systolic parameters. LV indicates left ventricular; and LVESD, LV end-systolic diameter.AQ3Kaplan–Meier curves for LV size parameters followed under medical management. (LVESD ≥40 mm blue line, <40 mm red line). Note the marked separation between curves maintained throughout the entire follow-up period in the LV end systolic parameters. LV indicates left ventricular; and LVESD, LV end-systolic diameter.

reduction in patients with disproportionate LV remodeling, (adjusted HR, 0.11 [95% CI, 0.005–0.51]; *P*=0.002) than in patients without (adjusted HR, 0.56 [95% CI, 0.34–0.88]; *P*=0.01), but this difference did not reach statistical significance (*P* value for interaction 0.20). To confirm the impact of mitral surgery on long-term outcome of patients with LVESD ≥40 mm, overall survival throughout follow-up was analyzed with mitral surgery as a time-dependent covariate and updating cohorts at each event time, using 3 months as time zero, which showed that early surgery was also associated with significant survival benefit (adjusted HR, 0.47 [95% CI, 0.33–0.68], *P*<0.0001) with this analytical approach.

DISCUSSION

In this large, international registry of less-than-severe DMR (mild or moderate), disproportionate LV remodeling with markedly enlarged LV size in excess to the grade of DMR is frequent, observed in approximately 12% to 17% of patients. Among various indicators of disproportionate LV remodeling with less-than-severe DMR, the main marker is, similarly to severe DMR, the presence of LVESD ≥40 mm, which is independently associated with increased mortality under medical management. Disproportionate LV remodeling is not linked to traditional factors, such as hypertension, coronary disease, or arrhythmia, but observed at increased frequency in patients with diabetes and larger bodies, but also with MVP-linked factors such as larger ERO and larger LA remodeling. The link of LVESD ≥40 mm with excess mortality following DMR diagnosis was strong and persisted in all subgroups and with comprehensive adjustment, particularly for LVEF. Although patients with moderate DMR and disproportionally enlarged LV are referred to mitral valve surgery at a higher rate, only a minority are ultimately referred for mitral surgery. Importantly, our observational data in moderate DMR suggest by all analyses, landmark or time dependent, reduction of mortality after early mitral surgery. This effect reinforces the possible link between the MVP/DMR and the excess mortality observed with disproportionate LV remodeling and suggests that the conduct of a randomized clinical trial of prompt mitral surgery in these patients may be in order.

MVP With LV Remodeled Disproportionately to the DMR Grade

LV ES enlargement in patients with severe DMR is assumed to be a consequence of the regurgitation.[14,15,17,32]

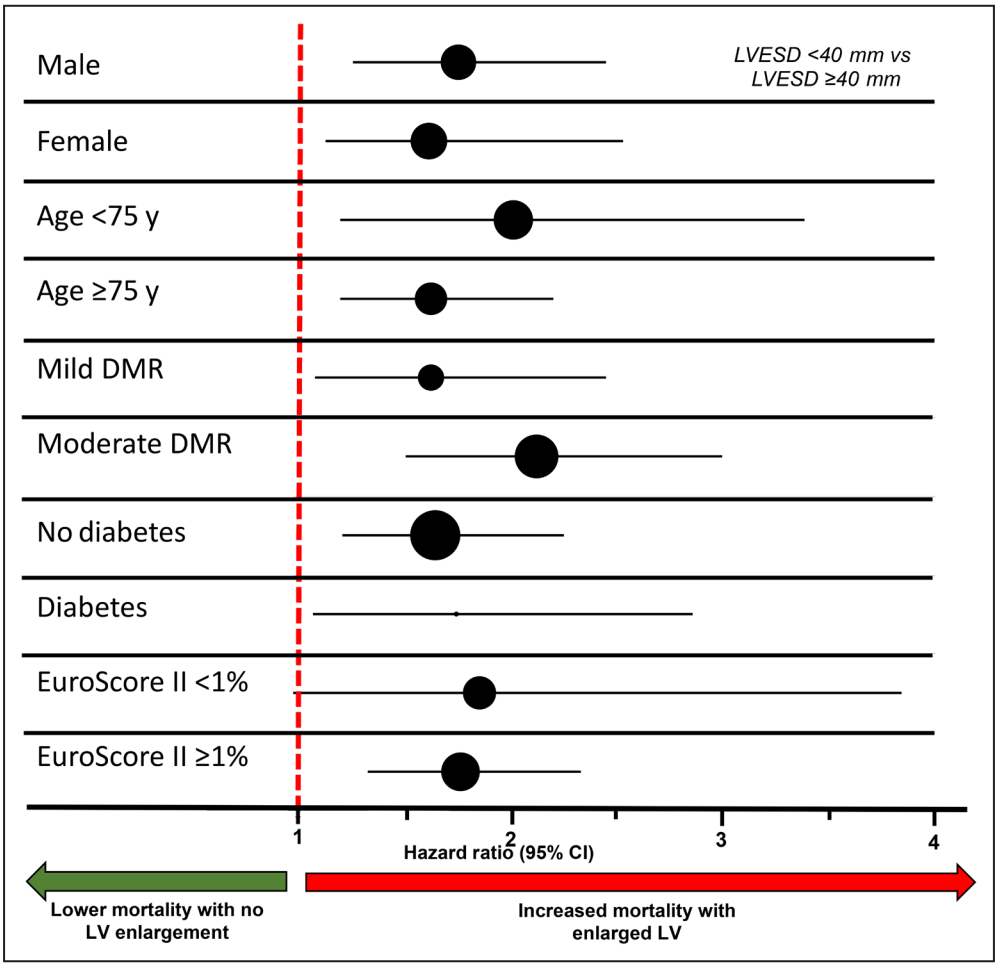

Figure 2. Forest plot of mortality under medical management.
Forest plot displaying the hazard ratio for mortality under medical management associated with LVESD ≥40 mm; adjusted for age, sex, dyspnea, effective regurgitant orifice, and EuroScore II; and stratified for clinical and echocardiographic features of patients with MVP. The size of the dots represents the prevalence of patients in a particular subgroup out of the entire cohort. DMR indicates degenerative mitral regurgitation; LV, left ventricle; LVESD, left ventricular end-systolic diameter; and MVP, mitral valve prolapse.

Thresholds for defining abnormal LV remodeling evolved progressively,[4,5,33] to include excessive ES LV dimension as a class I trigger for mitral valve surgery aimed at severe DMR. It has been assumed that patients with mild or moderate DMR cannot incur such LV remodeling. Nevertheless, disproportionate LV enlargement with MVP and less-than-severe DMR was episodically observed by noninvasive imaging.[18–20,24,34] Hence, a theory of "MVP cardiomyopathy" was hypothesized but never proven in a large cohort of MVP and with prospectively quantified DMR. In our cohort of ≤moderate DMR, disproportionately enlarged LV size was observed in 12% to 17% of patients. It is important to note that we excluded patients with functional MR, ≥moderate concomitant aortic valve disease, congenital heart disease, or active endocarditis that may have caused MVP-unrelated LV enlargement. Furthermore, our data show that disproportionate LV enlargement was unrelated to hypertension, coronary disease, or atrial fibrillation. Our study also shows that non-MVP factors may contribute to disproportionate LV remodeling. However, strong links to MVP factors such as larger ERO, larger LA, and the large beneficial effect of DMR surgical correction underscore the unique sequential relation between the mitral disease, the LV enlargement, and the mediocre clinical outcome. Although our data suggest that the excessive LV remodeling is linked to reduced LV elastance,[31] the link to MVP is not fully explained. First, genetic studies demonstrated that several MVP-linked genes are also linked to cardiomyopathies.[21] LV remodeling in MVP with mild DMR and ventricular arrhythmias even raised a "rhythmic MVP cardiomyopathy" hypothesis.[20,24] Another MVP-related cause of LV remodeling is myocardial fibrosis,

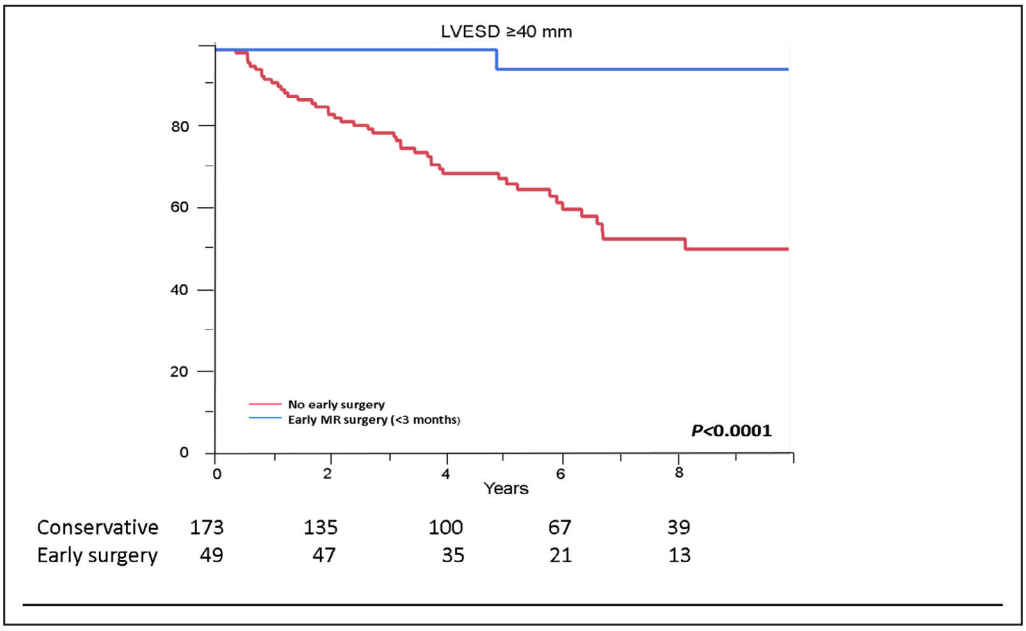

Figure 3. Survival stratified by early surgery (<3 months) in patients with moderate MR and LVESD ≥40 mm or <40 mm.
Kaplan–Meier curves for survival in patients with moderate MR and LVESD ≥40 mm (disproportionally enlarged LV), or LVESD <40 mm stratified by early surgery (<3 months) or conservative therapy. Note the marked separation between curves maintained throughout the entire follow-up period suggesting that early surgery improves survival in these patients. LV indicates left ventricle; LVESD, left ventricular end-systolic diameter; and MR, mitral regurgitation.

often detected by magnetic resonance imaging, even with less-than-severe DMR,[24] possibly mechanistically linked to MVP-induced papillary muscle traction.[35,36] A third MVP characteristic associated with LV enlargement unrelated to DMR is mitral annular disjunction[37] possibly through myocardial stretch and detachment.[38,39] The potential of large bileaflet prolapse with notable prolapse volume to induce LV enlargement[34] remains disputed.[34,36,40] In that regard, we did not observe a link between MVP type and disproportionate LV enlargement in the present cohort. Another theoretical MVP-related mechanism has been evoked as increasing DMR severity with exercise[41] but remains to be supported by quantitative data. Our study provides important new insights incremental to these previous MVP-specific hypotheses, based on the association of disproportionate LV emodeling with larger ERO, reemphasizing the volume overload contribution. Also, the larger LA may reflect a mechanical effect of LA enlargement on the LV, or a common myocardial alteration, warranting future studies. Thus, multiple MVP-related paths, even without severe DMR, may be linked to disproportionate LV remodeling, deserving future conduct of prospective genetic and multimodality imaging studies.[36,42] Irrespective of potential mechanisms linking MVP to disproportionate LV remodeling, our study shows that such LV alterations are relatively frequent, with the classical LVESD ≥40 mm present in 12.4% of ≤moderate DMR, warranting consideration for specific management of such patients.

Management of Less-Than-Severe DMR

Patients with MVP and less-than-severe DMR represent a clinical challenge. It has been named "progressive" and deemed as not warranting surgical indications or treatment in either US or European guidelines,[4,5] without mention of any exception. This "observational" management reflects a general concept that mild or moderate DMR is benign. This "uniformly benign" concept has been challenged by recent data. First, in a prospective cohort with DMR, we observed that moderate quantified DMR was associated with excess mortality and cardiovascular events.[8] This observation was confirmed in a large routine-practice cohort of isolated MVP.[43] Thus, recent data on DMR outcome do not confirm the "uniformly benign" nature of less-than-severe DMR and thus warrant extending our focus beyond severe DMR by assessing markers of outcomes throughout the spectrum of MVP and DMR. For example, severe ventricular arrhythmias are associated with excess mortality independent of DMR severity,[44] with consensus statements suggesting therapeutic interventions even in less-than-severe DMR.[45,46] Similarly, excess LA enlargement,[47,48] LA dysfunction,[49] or neurohormonal activation[26,50] are important predictors of

excess mortality, not confined to severe DMR but also affecting less-than-severe DMR. Similarly, the present study is the first to show that patients with disproportionate LV remodeling and less-than-severe DMR display excess mortality versus patients with similar DMR severity without disproportionate LV remodeling. This risk is observed even after adjustment for all possible confounders and in all subgroups, and even accounting for EF reduction logically associated with ES LV alterations. Of note, although disproportionate LV remodeling is associated with excess mortality in mild as well as moderate MR, it is clear that valve surgery should not be advocated in patients with mild MR and disproportionate LV remodeling because the basis for the cardiomyopathy/LV systolic dysfunction and dilatation in these patients is not volume overload and thus would not be expected to improve after mitral valve repair.

Thus, disproportionate LV remodeling, already a proven marker of poor outcomes in severe DMR,[14–17] is now proven to be associated with worse outcomes throughout the spectrum of DMR severity. The crucial question is whether therapeutic interventions can be indicated based on such observations. In that regard, the fact that in the current study, early mitral surgery in patients with moderate DMR and disproportionate LV remodeling was associated with improved survival generates the hypothesis that such treatment may be beneficial and should be evaluated in appropriate randomized clinical trials. Patients with only mild DMR may alternatively be considered for therapies that are effective to induce reverse LV remodeling.[51,52]

Strengths and Limitations

The registry involves high-volume, experienced tertiary centers with expertise in mitral valve repair. The concern that we may have underestimated DMR severity in our cohort is strongly countered by the fact that patients who underwent DMR quantitation with dual methods (proximal isovelocity surface area and quantitative Doppler) displayed excellent correlation for ERO and regurgitant volume (N=1117, $P<0.0001$), displaying in moderate DMR, ERO 28±6 mm^2 by PISA and 30±10 mm^2 by quantitative Doppler, and regurgitant volume 49±15 mL by proximal isovelocity surface area and 51±17 mL by quantitative Doppler. Furthermore, the classical marker of less-than-severe DMR, that is, regurgitant fraction <50%, was confirmed in 94.6% of our cohort. Additionally, we compared the outcomes of patients diagnosed with severe DMR during the same time frame in our institutions (N=2568) with the present cohort. Those with severe DMR had much higher mortality than our cohort (adjusted HR, 1.27 [95% CI, 1.09–1.49], $P=0.002$). Thus, these facts taken together demonstrate that our observations are not the fruit of DMR underestimation. Although prevalence of disproportionate LV remodeling in patients with ≤moderate DMR may reflect selection to academic referral centers, the present large cohort with MVP and quantified DMR allows affirming that such patients do exist and carry a poor prognosis. Although LV diameters may be a concern in evaluating LV remodeling, standard echocardiographic LV volume measurements are affected by notable underestimation and LVESD remains a class-I indication for surgery in valvular regurgitations in all guidelines.[4,5] Furthermore, the established link between LVESD ≥40 mm and survival of patients affected by severe DMR additionally legitimizes its use for characterizing disproportionate LV remodeling in less-than-severe DMR. We did not use a core laboratory in this study as these provide measurements made by few technicians, useful in randomized clinical trials, but that cannot be appropriate for routine clinical practice. Instead, we used the validated approach in cohort studies gathered in routine practice, the data prospectively measured at diagnosis, blinded to outcome, stored as reported, and retrieved unaltered, strongly linked to outcome and immediately applicable to routine clinical practice for management decisions in DMR. Nevertheless, the lack of a core laboratory to quantify and differentiate between mild and moderate MR and the lack of more accurate techniques such as cardiac magnetic resonance imaging may be a limitation. LV strain and quantitative parameters of right ventricular function were not obtained by the majority of the centers. The cause of death, rehospitalization rates, and repeated measurements to assess changes in LVEF, New York Heart Association classification, symptoms, biomarkers, or quality of life measures were not obtained by most of the centers, precluding a more comprehensive understanding of prognosis. Despite the use of statistical methods, the decision to refer to surgery may include selection bias due to possible residual, unaccounted confounders. Furthermore, other factors that prompted earlier surgery in patients undergoing early surgery may have confounded their improved outcomes. Our patients were not randomized to surgery and its impact on outcome should be carefully interpreted. A prospective, randomized trial will be needed to provide definite data regarding superiority of surgery in this context. Nevertheless, the observation that, among patients with moderate DMR and disproportionate LV remodeling, survival was much higher in patients promptly referred to mitral surgery suggests that such a clinical trial should be initiated.

CONCLUSIONS

A disproportionally enlarged LV in patients with less-than-severe DMR is relatively common, particularly in

patients with diabetes and large body surface area and in association with MVP-related factors such as larger ERO and larger LA. This pattern of excess LV remodeling disproportionate to the DMR is important to detect because it is independently associated with worse survival overall and in all possible subsets of patients, even after comprehensive adjustment and even accounting for LVEF. The clinical observation that patients with moderate DMR and disproportionate LV remodeling who are promptly referred to surgery enjoy superior outcomes over patients who are treated medically, underscores the need for stringent LV assessment by imaging. It also emphasizes consideration of mitral surgery in patients with confirmed disproportionate LV remodeling with the aim of designing randomized controlled trials to formally evaluate the benefit of early mitral interventions and address patients at high risk throughout the spectrum of DMR severity.

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Supplemental Material

Data S1
Tables S1–S9

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