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The MIDA-Q Mortality Risk Score: A Quantitative Prognostic Tool for the Mitral Valve Prolapse Spectrum

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BACKGROUND: Mitral valve prolapse (MVP) is responsible for a considerable disease burden but is widely heterogeneous. The lack of a comprehensive prognostic instrument covering the entire MVP spectrum, encompassing the quantified consequent degenerative mitral regurgitation (DMR), hinders clinical management and therapeutic trials.

METHODS: The new Mitral Regurgitation International Database Quantitative (MIDA-Q) registry enrolled 8187 consecutive patients (ages 63±16 years, 47% women, follow-up 5.5±3.3 years) first diagnosed with isolated MVP, without or with DMR quantified prospectively (measuring effective regurgitant orifice [ERO] and regurgitant volume) in routine practice of 5 tertiary care centers from North America, Europe, and the Middle East. The MIDA-Q score ranges from 0 to 15 by accumulating guideline-based risk factors and DMR severity. Long-term survival under medical management was the primary outcome end point.

RESULTS: MVP was associated with DMR absent/mild (ERO <20 mm^2) in 50%, moderate (ERO 20–40 mm^2) in 25%, and severe or higher (ERO ≥40 mm^2) in 25%, with mean ERO 24±24 mm^2, regurgitant volume 37±35 mL. Median MIDA-Q score was 4 with a wide distribution (10%–90% range, 0–9). MIDA-Q score was higher in patients with EuroScore II ≥1% versus <1% (median, 7 versus 3; $P < 0.0001$) but with wide overlap (10%–90% range, 4–11 versus 0–7) and mediocre correlation (R^2 0.18). Five-year survival under medical management was strongly associated with MIDA-Q score, 97±1% with score 0, 95±1% with score 1 to 2, 82±1% with score 3 to 4, 67±1% with score 5 to 6, 60±1% with score 7 to 8, 44±1% with score 9 to 10, 35±1% with score 11 to 12, and 5±4% with MIDA-Q score ≥13, with hazard ratio 1.31 [1.29–1.33] per 1-point increment. Excess mortality with higher MIDA-Q scores persisted after adjustment for age, sex, and EuroScore II (adjusted hazard ratio, 1.13 [1.11–1.15] per 1-point increment). Subgroup analysis showed persistent association of MIDA-Q score with mortality in all possible subsets, in particular, with EuroScore II<1% (hazard ratio, 1.08 [1.02–1.14]) or ≥1% (hazard ratio, 1.11 [1.08–1.13]) and with no/mild DMR (hazard ratio, 1.14 [1.10–1.19]) or moderate/severe DMR (hazard ratio, 1.13 [1.10–1.16], all per 1-point increment with $P<0.0001$). Nested-model and bootstrapping analyses demonstrated incremental prognostic power of MIDA-Q score (all $P<0.0001$).

CONCLUSIONS: This large, international cohort of isolated MVP, with prospective DMR quantification in routine practice, demonstrates the wide range of risk factor accumulation and considerable heterogeneity of outcomes after MVP diagnosis. The MIDA-Q score is strongly, independently, and incrementally associated with long-term survival after MVP diagnosis, irrespective of presentation, and is therefore a crucial prognostic instrument for risk stratification, clinical trials, and management of patients diagnosed with all forms of MVP.

Key Words: echocardiography ■ mitral valve insufficiency ■ mitral valve prolapse ■ survival

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Clinical Perspective

What Is New?

- The present registry gathers a large cohort from North America (United States) and Europe/Middle East (France, The Netherlands, and Israel) of patients diagnosed with isolated mitral valve prolapse in routine clinical practice of academic centers with prospective degenerative mitral regurgitation quantitation, in whom the Mitral Regurgitation International Database Quantitative (MIDA-Q) score was calculated on the basis of characteristics collected in routine practice.
- The MIDA-Q score combines the established MIDA score, integrating guideline-based markers of outcome with scoring points based on degenerative mitral regurgitation quantitation.
- This new MIDA-Q risk score is associated with an extreme range of predicted survival under medical management, from 97% to 5% at 5 years for the extreme score ranges, and is strongly, independently, and incrementally associated with long-term survival, over all standard markers of outcome.

What Are the Clinical Implications?

- The MIDA-Q score as a marker of mitral valve prolapse outcome is immediately and extensively usable in routine practice for all forms of mitral valve prolapse.
- The MIDA-Q score should allow integrated risk assessment of patients with mitral valve prolapse to refine clinical decision making in routine practice and ultimately reduce degenerative mitral regurgitation undertreatment.
- Future studies of large magnitude focusing on other proven predictors of mortality in degenerative mitral regurgitation could ultimately expand the MIDA-Q score.

Nonstandard Abbreviations and Acronyms

DMR	degenerative mitral regurgitation
ERO	effective regurgitant orifice
MIDA-Q	Mitral Regurgitation International Database Quantitative
MVP	mitral valve prolapse

Mitral valve prolapse (MVP) represents a considerable health burden, affecting ≈6 million people in the United States[1] and linked to mitral regurgitation, the most frequent valve disease.[2] MVP directly causes degenerative mitral regurgitation (DMR), the most frequent cause of organic mitral regurgitation in developed countries,[3] and is a progressive valve disease with progression of anatomic lesions[4] and of DMR over time.[5,6] Despite this considerable health burden, MVP is only briefly mentioned in clinical guidelines for the management of valvular diseases, considered mostly under the heading of severe mitral regurgitation.[7,8] This limited attention is based on the concept that MVP, in general, is benign[9] and causes clinically significant complications essentially with severe DMR.[10] Because early repair of severe DMR is associated with improved outcome,[11] clinical guidelines suggest that prompt valve repair of severe MVP-related DMR[7,8] may be acceptable for patients at low risk for surgery. However, this simplistic approach solely focused on severe DMR has been challenged on multiple fronts.

Recent studies have shown that, along the MVP spectrum, risks are not confined to severe DMR in a binary manner, but that DMR is a continuum whereby each increment of DMR severity is associated with outcome worsening.[12] Furthermore, excess risk does not appear only for severe DMR but is initiated with DMR superficially referred to as moderate.[12,13] Although the concept of early surgery for DMR is attractive and recommended, the population affected is elderly, in general, and incurs higher interventional risks, but the profound undertreatment and excess mortality[3] may relate to poor appreciation of risk under medical management. To address this management complexity, the MIDA risk score has been validated to fulfill the crucial risk grading under medical management, but it applies only to patients with severe (even very severe) DMR.[14] Another risk incurred is arrhythmic, underscored in recent cohorts of MVP,[15] even without DMR, and potentially culminating in sudden death.[16,17] Last, although not all therapies for MVP are fully tested, new, less invasive transcatheter methods of treatment of DMR have been developed that may improve DMR outcome[18] and may conceptually be applicable to less severe DMR.[19]

Therefore, it is essential to develop a mortality risk score applicable to all patients with MVP and incorporating the quantitative DMR assessment (combined with standard risk markers) across the entire MVP spectrum. In that endeavor, an important consideration is inclusion, not limited to patients examined by experts and not limited to US or large institutions, of a large cohort of MVP with DMR quantitation in routine practice of academic centers and in various institutions and regions of the world.

For this purpose, we formed the new Mitral Regurgitation International Database Quantitative (MIDA-Q) registry enrolling consecutive patients with isolated MVP without or with DMR, consistently quantified prospectively in routine practice of each center. We hypothesized that enriching the MIDA score by DMR, quantitative measures with calculation of the MIDA-Q score would provide an independent and incremental predictor of clinical outcome under medical management overall and in all possible MVP subsets.

METHODS

The data that support the findings of this study will not be made available to other researchers because the data-sharing agreement does not allow it.

Patients

The MIDA-Q registry was created by combining the consecutive experience regarding eligible patients with isolated MVP without or with DMR, quantified prospectively in routine practice, of tertiary care centers from North America (Mayo Clinic, Rochester, MN), Europe (Amiens, France; Nantes, France; Genetic and Phenotypic Characteristics of Mitral Valve Prolapse, NCT03884426, Leiden, The Netherlands) and the Middle East (Tel Aviv, Israel). The study was conducted in accordance with institutional review board guidelines, national legal requirements, and the revised Helsinki Declaration. The study was approved by the Mayo Clinic Institutional Review Board, and, in view of the low-risk nature of the study, the written consent requirement was waived.

Eligibility criteria involved all consecutive patients: (1) adults ≥18 years of age; (2) with MVP defined by transthoracic echocardiography using the 2-mm minimum depth criterion, without or with flail segment and without or with DMR; (3) first diagnosed between 2003 and 2020; (4) with DMR quantified prospectively at diagnosis by Doppler echocardiography irrespective of the DMR grade; (5) with comprehensive echocardiographic assessment at diagnosis; and (6) with comprehensive clinical evaluation of symptoms, vital signs, clinical history, comorbidities, and cardiac rhythm at diagnosis. We excluded patients (1) denying research authorization, (2) without DMR quantification, or (3) with moderate to severe aortic regurgitation/stenosis, moderate to severe mitral stenosis, congenital heart disease (patent foramen ovale not excluded), dilated/hypertrophic/restrictive cardiomyopathies, previous valvular surgery, and significant pericardial disease. Thus, the MIDA-Q registry is distinct from the original MIDA registry in terms of inclusion criteria, population examined, and methods applied.[14]

Echocardiographic Evaluation

Echocardiographic examination was performed in routine clinical practice and all echocardiographic data (qualitative and quantitative) in all centers were measured prospectively at diagnosis, stored as reported in their echocardiographic repositories, and extracted from the respective digital repositories as originally/prospectively stored without modification. Imaging uniform protocol included all views from standard windows and systematic left ventricular (LV) and hemodynamic measurements guided by American Society of Echocardiography recommendations.[20] Using guideline-recommended methods, DMR Doppler-echocardiographic quantitation measured effective regurgitant orifice (ERO) and regurgitant volume that were categorized as null if there was no or trace DMR by standard color flow imaging. In addition, DMR was also graded by a guideline-recommended 4-grade scale: none/trivial, mild, moderate, and severe. The MIDA-Q score was calculated on the basis of the clinical variable points defined by the original MIDA score[14] summated to the points obtained from DMR quantitative measures of ERO area (Table 1).

Table 1. MIDA-Q Score Calculation

Characteristic	No. of points
Age ≥65 y	3
New York Heart Association ≥III	3
Atrial fibrillation	1
Left atrium volume index ≥60 mL/m² or left atrial diameter ≥55 mm	1
Systolic pulmonary artery pressure ≥50 mm Hg	2
Left ventricular end-systolic diameter ≥40 mm	1
Left ventricular ejection fraction <60%	1
Effective regurgitant orifice, mm²	
<20	0
20–40	1
40–60	2
>60	3

MIDA-Q indicates Mitral Regurgitation International Database Quantitative.

Clinical Evaluation

Patients' histories, symptoms (dyspnea, edema, chest pain), and comorbidities were recorded at diagnosis by the patients' personal physicians in routine practice and electronically retrieved from electronic medical records without alteration. The EuroScore II was calculated using all specified characteristics at MVP diagnosis and with a plan of elective single-valve/non–coronary artery bypass graft surgery, as a measure of surgical risk and combined comorbidities.[21] Vital signs were measured at echocardiography.

Outcome

The outcome examined was the most robust all-cause mortality after diagnosis, with events 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) databases of vital status. The primary end point was long-term survival under medical management. Secondary end points were overall and postoperative survival. Surgical procedures were collected and dated using institutional surgical registries and clinical notes for patients operated on outside their respective institutions. Outcomes were ascertained by investigators blinded to baseline characteristics.

Statistical Analysis

Continuous variables were expressed as mean±SD or median (interquartile range) and categorical variables as percentages with comparisons between groups using ANOVA, Wilcoxon test, or χ^2 as appropriate. The MIDA-Q score was calculated for each patient on the basis of components and coefficients included in standard MIDA score previously validated in different cohorts (age ≥65 years, left atrial volume ≥60 mL/m² or left atrial diameter ≥55 mm, ejection fraction ≤60%, left ventricular end-systolic diameter ≥40 mm, heart failure symptoms, atrial fibrillation, and right ventricular systolic pressure ≥50 mm Hg) combined with points related to DMR quantification shown in Table 1. As previously validated, age ≥65 years and New York Heart Association ≥III counted 3 points, systolic pulmonary

artery pressure ≥50 mm Hg counted 2 points, and atrial fibrillation presence, left atrium volume index ≥60 mL/m^2 or left atrial diameter >55 mm, LV end-systolic diameter ≥40 mm, and LV ejection fraction <60% counted 1 point. For DMR quantitation, ERO 20 to 40 mm^2 counted 1 point, ERO 40 to 60 mm^2 counted 2 points, and >60 mm^2 counted 3 points, whereas ERO <20 mm^2 counted no additional point on the basis of the linear association between mitral regurgitation quantification and excess mortality (Table S1).[12] The MIDA-Q score was analyzed mainly as a continuous variable using its full range (0–15) and, for practical display, segmented into 8 narrow categories (scores 0, 1–2, 3–4, 5–6, 7–8, 9–10, 11–12, and 13–15). To ensure appropriate power for secondary multivariable analysis and subgroup display, MIDA-Q score was also analyzed/displayed using wider-range categories of score 0–2, 3–8, and ≥9. Survival rates (±SE) were estimated using the Kaplan-Meier method and compared using the log rank test. Cox proportional hazards models assessed MIDA-Q association with long-term mortality with 3 models examined: unadjusted; adjusted for age, sex, and EuroScore II; and adjusted for DMR characteristics or comorbidities. In clinical practice, all variables may not be innately measurable in all patients (eg, systolic pulmonary pressure in patients without tricuspid regurgitation), even with most comprehensive evaluation. Proportional hazards assumption was verified using Schoenfeld residuals (P=0.19). The MIDA score clinical relevance is based on positive identification, only counting points for definably abnormal characteristics and not counting points when the variable considered is below threshold or not measurable.[14] Thus, for MIDA-Q score calculation, the same clinical principle was applied as main analysis. However, to verify that this clinically based algorithm does not affect results, an alternative analysis was conducted using multiple imputations to account for missing variables. Bootstrapping was used to verify the stability of the association of MIDA-Q score with long-term survival (see Supplemental Material for additional details). The incremental prognostic value of MIDA-Q was assessed by nested models and calculation of Harrell C statistics derived from the bootstrapping procedure. JMP14, SAS9.4, and R software were used. Two-tailed P<0.05 was considered significant.

RESULTS

Baseline Characteristics

Among 10910 patients diagnosed between 2003 and 2020 with isolated degenerative mitral valve disease, 2723 were excluded because of the lack of DMR severity quantification (Figure S1). Thus, all consecutive patients diagnosed with isolated MVP with any degree of DMR (none to most severe) with prospective DMR quantification in routine practice included in the final cohort encompassed 8187 patients (47% women, age 63±16 years). Among them, 3914 patients (48%) were from North America (United States), and 4273 (52%) were from Europe/Middle East with 1394 (17%) from France, 491 (6%) from The Netherlands, and 2388 (29%) from Israel. Baseline demographic/clinical characteristics (Table 2) are typical for a wide MVP spectrum, with bileaflet prolapse in 4606 (56%), posterior prolapse in 2822 (34%), and flail leaflet in 1431 (18%). By quantitative grading, DMR was absent/mild (ERO <20 mm^2) in 50%, moderate (ERO 20–40 mm^2) in 25%, and severe or above (ERO ≥40 mm^2) in 25%, with overall ERO averaging 24±24 mm^2 and regurgitant volume 37±35 mL. Mitral regurgitation severity was almost identical by geographical origin, with ERO 0.24±0.24 cm^2 in the United States and 0.24±0.23 cm^2 in Europe/Middle East (France, The Netherlands, Israel). Clinically, 36% had dyspnea, 38% hypertension, 15% atrial fibrillation, and 4% previous coronary artery bypass graft; EuroScore II was 1.80±1.83% (median, 1.1%). On average, LV dilatation was mild, LV ejection fraction was 62±8%, and left atrium volume index was 52±24 mL/m^2. MIDA-Q scores were overall 4.8±3.3 with wide distribution (median, 4 with 10%–90% range, 0–9) and is shown stratified by categories in Table 2.

The right part of Table 2 shows baseline characteristics compared using the classic EuroScore II, between patients classified as low operative risk (EuroScore II<1, n=4790) and higher operative risk (EuroScore II≥1, n=3326) by guideline-driven cutoff (Table S2 displays baseline characteristics stratified by median MIDA-Q score). Although almost all variables display statistical difference attributable to the cohort's considerable size, the most clinically relevant variables regard female predominance and older age (with corollary more frequent atrial fibrillation and risk factors) in the higher operative risk group. Therefore, it is not surprising that the MIDA-Q score is higher in patients with higher EuroScore II, but the distribution of MIDA-Q score categories shows wide overlap between EuroScore II groups (median, 7 and 10%–90% range, 4–11 for EuroScore II≥1%, and median, 3 and 10%–90% range, 0–7 for EuroScore II<1%). Thus, although displaying an association, MIDA-Q and EuroScore II are quite distinct (R^2 0.18). In contrast, in the higher surgical risk subset, differences in DMR severity and cardiac remodeling (apart from slightly bigger left atrium and lower ejection fraction) are mostly of little clinically relevant magnitude. Thus, these baseline characteristics underscore the complexity of patients with MVP attributable to the conjunction in the same patients of markers for higher risk both under medical management and for DMR surgical correction.

Long-Term Outcome Under Medical Management

Overall mean follow-up was 5.5±3.3 years, during which 2611 (32%) patients underwent mitral valve surgery (90% repair, 10% replacement: 32% in the United States and 32% in Europe/Middle East) and 1811 died, mostly under medical management (n=1489) and more rarely any time after mitral valve surgery (n=322). Surgical correction of DMR was performed predominantly

Table 2. Baseline Characteristics

Characteristics	Overall population	EuroScore II <1%	EuroScore II ≥1%	*P* value
Clinical characteristics				
Age, y	63±16	54±14	78±10	<0.0001
Female, %	47	39	55	<0.0001
Body mass index, kg/m²	25±5	25±5	25±6	0.002
Heart rate, bpm	68±14	69±13	73±16	<0.0001
Systolic blood pressure, mm Hg	121±18	119±16	126±20	<0.0001
Diastolic blood pressure, mm Hg	70±11	71±10	69±12	<0.0001
Atrial fibrillation, %	15	8	30	<0.0001
Previous coronary artery bypass graft, %	4	1	4	<0.0001
Hypertension, %	38	28	53	<0.0001
Dyspnea, %	36	31	45	<0.0001
EuroScore II, %	1.80±1.83	0.68±0.14	2.37±1.80	<0.0001
MIDA-Q score	4.8±3.3	3.3±2.7	6.9±2.8	<0.0001
LV and hemodynamic characteristics				
LV end-diastolic diameter, mm	52±7	53±7	51±7	<0.0001
Indexed LV end-diastolic diameter, mm/m²	29±4	28±4	29±4	<0.0001
LV end-systolic diameter, mm	33±6	33±6	33±7	0.3
Indexed LV end-systolic diameter, mm/m²	18±4	18±3	19±4	<0.0001
LV ejection fraction, %	62±8	64±7	59±10	<0.0001
Left atrium volume index, mL/m²	52±24	44±23	57±26	<0.0001
Left atrial diameter, mm	42±9	40±9	45±8	<0.0001
Mitral characteristics				
Effective regurgitant orifice, mm²	24±24	24±24	25±21	0.02
<20 mm², n (%)	4067 (50)	2465 (52)	1556 (47)	
20–40 mm², n (%)	2073 (25)	1047 (21)	1009 (31)	
40–60 mm², n (%)	1338 (16)	821 (17)	512 (15)	
>60 mm², n (%)	709 (9)	457 (10)	249 (7)	
Regurgitant volume, mL	37±35	35±35	41±32	<0.0001
Flail leaflet, n (%)	1431 (18)	821 (18)	602 (19)	0.3
Bileaflet, n (%)	4606 (56)	2360 (49)	2175 (65)	<0.0001
Posterior, n (%)	2822 (34)	1937 (40)	885 (27)	<0.0001
MIDA-Q score categories distribution, n (%)				
0 (score 0)	851 (10)	838 (17)	13 (0.4)	<0.0001
1 (score 1–2)	1301 (16)	1215 (25)	86 (2)	
2 (score 3–4)	2043 (25)	13”0 (28)	7&3 (21)	
3 (score 5–6)	1581 (19)	780 (17)	781 (23)	
4 (score 7–8)	1273 (16)	426 (9)	847 (25)	
5 (score 9–10)	718 (9)	167(3)	551 (16)	
6 (score 11–12)	331 (4)	46 (1)	285 (9)	
7 (score 13–15)	89 (1)	9 (0.2)	80 (2)	

LV indicates left ventricle; and MIDA-Q, Mitral Regurgitation International Database Quantitative.

early after diagnosis (surgical rate 26% at 6 months, 29% at 1 year, and 33% at 5 years), and mortality within 30 days after mitral valve surgery was 0.9%. Survival under medical management was 84±1% at 2 years and 72±1% at 5 years. MIDA-Q, as a continuous variable, was strongly associated with long-term mortality (univariable hazard ratio, 1.31 [1.29–1.33], *P*<0.0001 per 1-point score increment; Table 3), with sustained and continuous excess mortality increase with MIDA-Q score increment by spline curve analysis (Figure S2). Thus, in

Table 3. Univariable and Multivariate Hazard Ratio of Mortality Under Medical Management Attached to MIDA-Q Score

Variable	MIDA-Q score	Mortality under medical treatment	
		Hazard ratio [95% CI]	*P* value
Univariable	Per-1 score	1.31 [1.29–1.33]	<0.0001
	≥9*	20.78 [16.51–26.16]	<0.0001
	3-8*	7.57 [6.15–9.31]	<0.0001
Adjusted on age, sex, and EuroScore II	Per-1 score	1.13 [1.11–1.15]	<0.0001
	≥9*	2.70 [2.04–3.57]	<0.0001
	3-8*	1.66 [1.30–2.13]	<0.0001

MIDA-Q indicates Mitral Regurgitation International Database Quantitative.
*Versus Q-score category ≤2.

the overall MIDA-Q cohort (n=8187 patients), 5-year survival under medical management stratified by MIDA-Q score was 97±1% with score 0, 95±1% with score 1 to 2, 82±1% with score 3 to 4, 67±1% with score 5 to 6, 60±1% with score 7 to 8, 44±1% with score 9 to 10, 35±1% with score 11 to 12, and 5±4% with MIDA-Q score ≥13 (P<0.0001; Figure 1). Hence, 5-year mortality ranged from 3% with MIDA-Q score 0 to 95% with MIDA-Q score ≥13. Stratified by wider-span MIDA-Q ranges, 5-year survival under medical management with MIDA-Q score 0 to 2, 3 to 8, and ≥9 was 96±1%, 64±1%, and 39±4%, respectively (P<0.0001). Using these wider MIDA-Q score ranges, the univariable hazard ratio for mortality was 20.78 [15.5–26.16] for MIDA-Q score ≥9 versus ≤2 and 7.57 [6.15–9.31] for MIDA-Q score 3–8 versus ≤2, both P<0.0001 (Table 3).

Adjustment in multivariable analysis did not affect the MIDA-Q score predictive power for mortality. Adjusting for age and sex, the adjusted hazard ratios attached to MIDA-Q were highly significant 1.14 [1.12–1.16] per 1-point increment, 2.63 [1.99–3.47] for MIDA-Q score ≥9 versus ≤2 and 1.47 [1.15–1.88] for MIDA-Q score 3 to 8 versus ≤2, all P<0.0001. Further adjustment for EuroScore II did not affect MIDA-Q score significance with adjusted hazard ratios attached to MIDA-Q 1.13 [1.11–1.15] per 1-point increment, 2.70 [2.04–3.57] for MIDA-Q score ≥9 versus ≤2 and 1.66 [1.30–2.13] for MIDA-Q score 3 to 8 versus ≤2, all P<0.0001 (Table 3). Further adjustment for leaflet prolapse location and history of myocardial infarction did not alter the strong association of the MIDA-Q score with mortality, adjusted hazard ratio 1.07 [1.04–1.11] per 1 unit, P<0.0001.

Stratification by EuroScore II<1 or ≥1 emphasized MIDA-Q score incremental prognostic over this previously established risk score, showing a similar trend for increase in mortality with MIDA-Q increment (Figure 2). Five-year survival with EuroScore II<1 was 96±1% for MIDA-Q score 0–2, 88±1% for MIDA-Q score 3 to 8, and 77±8% for MIDA-Q score ≥9 (P<0.0001). In patients with EuroScore II ≥1, these were, respectively, 85±5% for MIDA-Q score 0 to 2, 61±1% for MIDA-Q score 3 to 8, and 37±3% for MIDA-Q score 9 to 15, P<0.0001. This strong survival association of MIDA-Q with mortality risk in each stratum of EuroScore II was confirmed in stratified multivariable analysis. Accordingly, adjusted hazard ratios for mortality attached to MIDA-Q score (per 1 increment) were 1.08 [1.02–1.14] with EuroScore II<1 and 1.11 [1.08–1.13] with EuroScore II≥1 (both P<0.0001), underscoring the strong, independent, and incremental value of the MIDA-Q score over the established risk assessment based on EuroScore II for MVP risk stratification (Figure 2).

MIDA-Q Score Link to Outcome in MVP Subgroups

To verify the association of MIDA-Q score with mortality after diagnosis in all possible subsets, forest plot analysis was performed. Hazard ratios for mortality attached to 1-point increment of MIDA-Q score are presented for multiple MVP subgroups on the basis of clinical and echocardiographic variables (Figure 3). A higher MIDA-Q score was invariably associated with worse survival in all subsets. This association was strong and significant in women and men, with age ≥75 years or lower, in the presence or absence of comorbidities such as hypertension or coronary artery disease, and regardless of geographic origins (United States versus Europe/Middle East: France, The Netherlands, and Israel). Increased MIDA-Q score remained independently associated with excess mortality irrespective of integrative DMR grades (no/mild or moderate/severe) and of the prolapsing leaflet (all P<0.0001).

Kaplan-Meier curves for MIDA-Q score wide-range strata (≤2, 3–8, ≥9) were also constructed in clinically relevant subsets. As expected, lower survival was observed with moderate/severe DMR by integrative DMR grading (5 year 70±1% versus 83±1% in no/mild DMR, adjusted hazard ratio, 1.21 [1.09–1.35], both P≤0.0004). Also expected were the differences in MIDA-Q score distribution in these DMR subsets (45% with score 0–2, 52% with score 3–8, 2.4% with score ≥9 in no/mild DMR versus, respectively, 21%, 69%, and 11% in moderate/

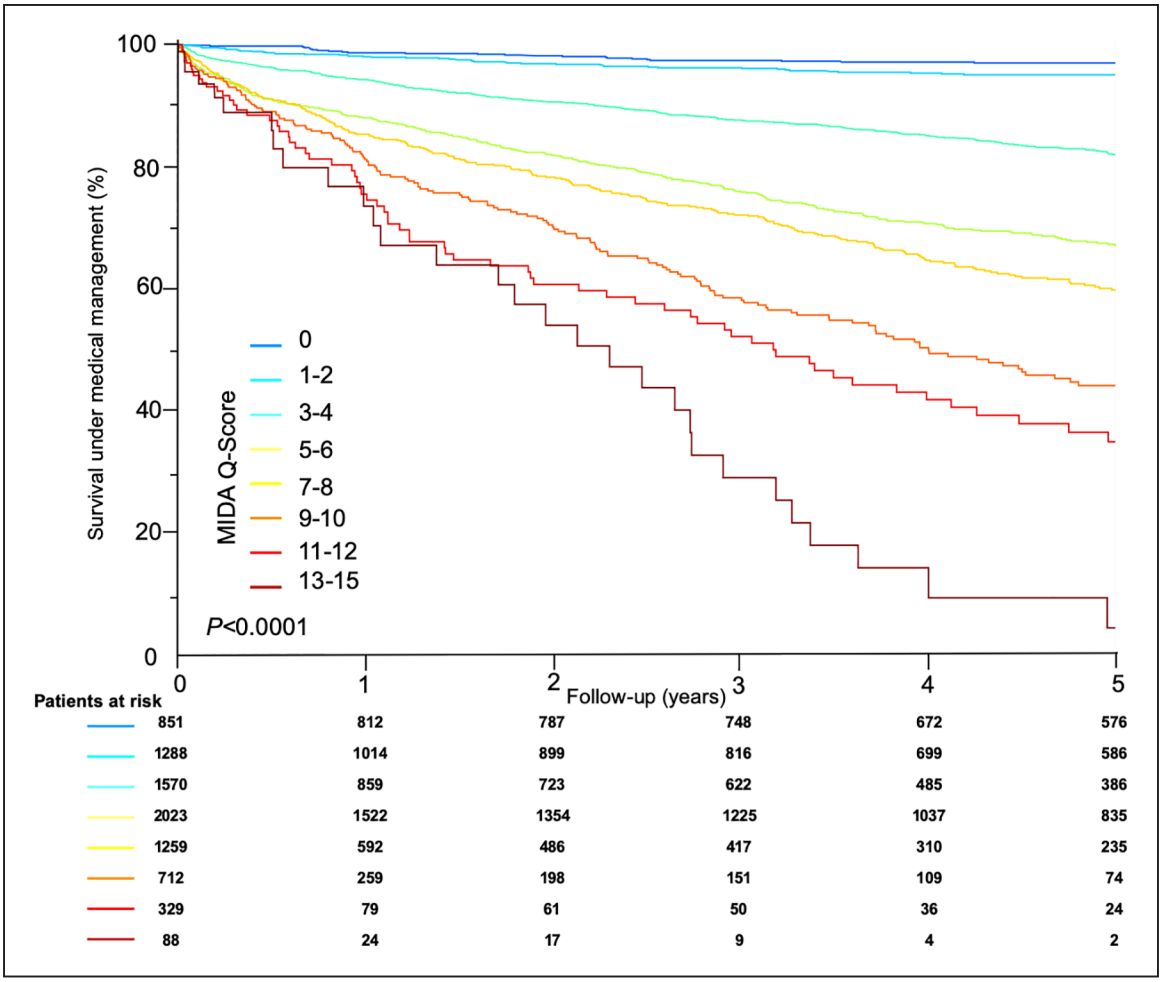

Figure 1. Survival stratified by MIDA-Q score categories.
Kaplan-Meier curves for the various MIDA-Q score categories (0–15) followed under medical management. Note the marked separation between curves maintained throughout the entire follow-up period and the considerable mortality associated with higher MIDA-Q scores. MIDA-Q indicates Mitral Regurgitation International Database Quantitative.

severe DMR, $P<0.0001$). However, most important, survival analysis showed that MIDA-Q score link to mortality was maintained in any DMR stratum, as shown by the hazard ratio per point in Figure 3 and by the considerable survival differences by wide-range MIDA-Q score categories in each stratum of DMR severity (Figure 4). Accordingly, with comprehensive adjustment, the hazard ratio was 1.14 [1.10–1.19], $P<0.0001$ per 1-point MIDA-Q score increment in the 3290 patients with no/mild DMR, and 1.13 [1.10–1.16], $P<0.0001$ in the 4826 patients with moderate/severe DMR. Thus, accounting for higher mortality associated with higher DMR grades, the MIDA-Q score is predictive of mortality in patients with MVP throughout the entire range of DMR severity.

Stratification by MVP anatomy (leaflet affected) similarly showed persistent association between increased MIDA-Q score and outcome (Figure 5 per stratum, Figure 3 per point). Adjusted hazard ratios for mortality attached to MIDA-Q score (per 1 increment) were 1.15 [1.10–1.20] with posterior MVP and 1.12 [1.09–1.15] with nonposterior MVP, both $P<0.0001$.

Also, stratification by patients' origin (United States versus Europe/Middle East: France, The Netherlands, and Israel) showed that higher MIDA-Q scores were associated with higher mortality irrespective of the institution location (Figure 6 per stratum, Figure 3 per point) and adjusted hazard ratios for mortality attached to MIDA-Q score (per 1 increment) were 1.16 [1.12–1.20], $P<0.0001$ in US patients and 1.07 [1.04–1.10], $P<0.0001$, in European/Middle Eastern patients.

Incremental Prognostic Value of MIDA-Q Score Over MIDA Score

MIDA-Q score incremental power for predicting mortality, over other determinants of outcome, was demonstrated by several approaches: First, nested Cox proportional hazards models were used sequentially. The addition of MIDA-Q to models with the end point of mortality under medical management significantly increased the power of these models over those formed by age and sex ($P<0.0001$); age-, sex-, and guideline-based triggers

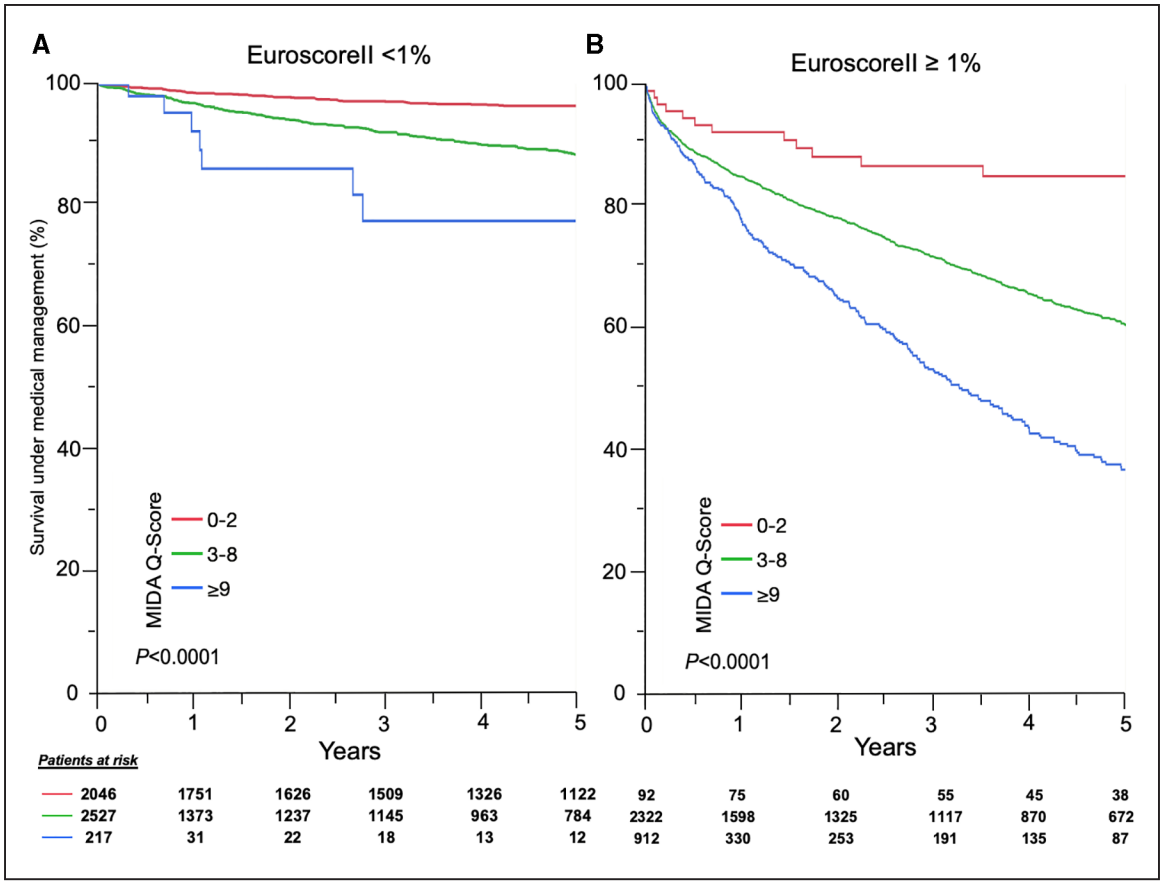

Figure 2. Survival associated with MIDA-Q score stratified by EuroScore II.
Kaplan-Meier survival curves for the range of MIDA-Q scores in patients with low (**A**) and higher operative risk (**B**). In both subgroups, increasing MIDA-Q score is associated with excess long-term mortality. MIDA-Q indicates Mitral Regurgitation International Database Quantitative.

of class I and II ($P<0.0001$, χ^2 for MIDA-Q 44.4 versus 8 for class I and 7 for class II); age, sex, and EuroScore II ($P<0.0001$ for incremental power with final χ^2 for MIDA-Q 116 versus 114 for EuroScore II); and over combined age, sex, class I and II triggers and EuroScore II ($P<0.0001$). MIDA-Q even provided incremental power over the traditional MIDA score alone (Figure S3, $P<0.0001$). Furthermore, the Harrell C statistic was 0.665 [0.581–0.693] for MIDA-Q score versus 0.578 [0.552–0.614] for MIDA score alone. Last, Cox proportional comprehensively adjusted hazard ratios for excess mortality under medical management derived from bootstrapping procedure was higher for MIDA-Q score (1.16 [1.15–1.18], per 1-point score) than for MIDA score alone (1.07 [1.06–1.08], both $P<0.0001$). Hence, MIDA-Q score provides incremental predictive power over all markers of outcome applicable to MVP and DMR.

Overall and Post–Mitral Surgery Outcome

Overall survival (including postoperative survival) was 86±1% at 2 years and 77±1% at 5 years (Figure S4), with persisting strong and independent link to MIDA-Q score adjusted hazard ratio of 1.06 [1.04–1.07] per 1 point and 1.51 [1.18–1.92] for MIDA-Q score ≥9 versus ≤2, all $P<0.0001$. In models with an end point of overall mortality MIDA-Q score provided incremental predictive power (all $P<0.0001$).

Mitral valve surgery was associated with reduced mortality (postoperative survival 97±1% at 2 years and 91±1% at 5 years). After mitral surgery, 1-year mortality with score categories 0 to 2, 3 to 8, and ≥9 was 0%, 1%, and 8%, respectively, and 5-year postoperative survival was 99±1%, 94±1%, and 82±2% (all $P<0.0001$) better than under medical management but without completely alleviating excess mortality attached to MIDA-Q score increment (adjusted hazard ratio, 1.10 [1.05–1.15], per 1 score, $P<0.0001$). Five-year overall survival was 94±1% for mitral valve repair and 78±1% for mitral valve replacement (Figure S5) with a persisting strong and independent link of the MIDA-Q score to mortality after both types of surgical treatment (adjusted hazard ratio, 1.09 [1.04–1.16] per 1 point for mitral valve repair, and 1.22 [1.10–1.36] per 1 point for mitral valve replacement, all $P<0.0001$). The effect of early surgery on improved survival was considerable and consistent in every range of MIDA-Q score (all $P<0.0001$) with no detectable interaction with the ranges of the MIDA-Q

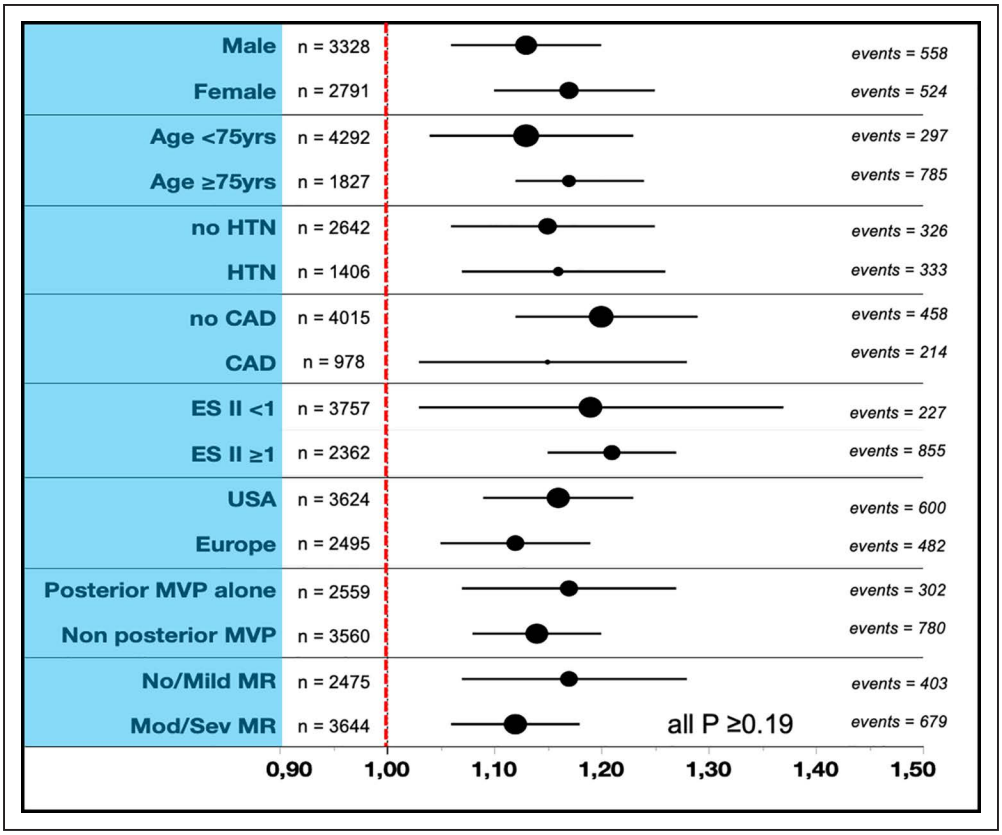

Figure 3. Forest plot under medical management.
Forest plot displaying the hazard ratio for mortality under medical management associated with MIDA-Q score per 1-point increment, stratified for the most important clinical and echocardiographic features of MVP patients. CAD indicates coronary artery disease; ES II, EuroScore II; HTN, hypertension; MIDA-Q, Mitral Regurgitation International Database Quantitative; MR, mitral regurgitation; and MVP, mitral valve prolapse.

score (*P*=0.16). In the subgroup of patients with moderate/severe MR, postoperative survival analysis suggests a survival benefit of mitral surgery for each MIDA-Q score subgroup versus medical management (Figure S6). Last, adjusted comparison of postoperative survival was not different between centers (*P*=0.29 overall and all *P*≥0.10 between individual centers).

DISCUSSION

The present series, gathering a large cohort focusing on isolated MVP, examined in routine practice with prospective quantitative DMR assessment, from an international cooperation involving North America (United States) and Europe/Middle East (France, The Netherlands, and Israel), provides unique insight into MVP outcome and into the wide-ranging prediction of survival after diagnosis. The MIDA-Q score, combining the established MIDA score integrating guideline-based markers of outcome with scoring based on DMR quantification, allows us to cover the entire span of the MVP spectrum. It is most important that the MIDA-Q score at diagnosis is strongly and independently associated with long-term survival under medical management after MVP diagnosis. Of note, the modest association with surgical risk markers such as EuroScore II yields that the MIDA-Q score remains strongly and independently determinant of survival in all subsets, particularly those based on low or higher EuroScore II, but also those based on age, sex, DMR grade, MVP anatomy, or geographical origin. Thus, the MIDA-Q score proves widely applicable and highly predictive of mortality under medical management over the entire span of MVP heterogeneity and in all possible circumstances/subsets that are analyzable. MIDA-Q score prediction of survival after MVP diagnosis is also incremental to all standard markers of outcome and remains effective after mitral surgery. Thus, MIDA-Q score as a marker of MVP outcome is extensively usable in routine practice and for all MVP forms. Although not all therapies for MVP are fully tested, the MIDA-Q score should allow fully integrated risk assessment of these patients for clinical trials and decision making.

MVP Heterogeneity

MVP is a heritable valvular heart disease associated with multiple different genes and pathways.[22,23] This recent observation fits fully with the observation that MVP can be anatomically affecting different leaflets,[10] with or without flail segment, with or without scallop indentation,[24]

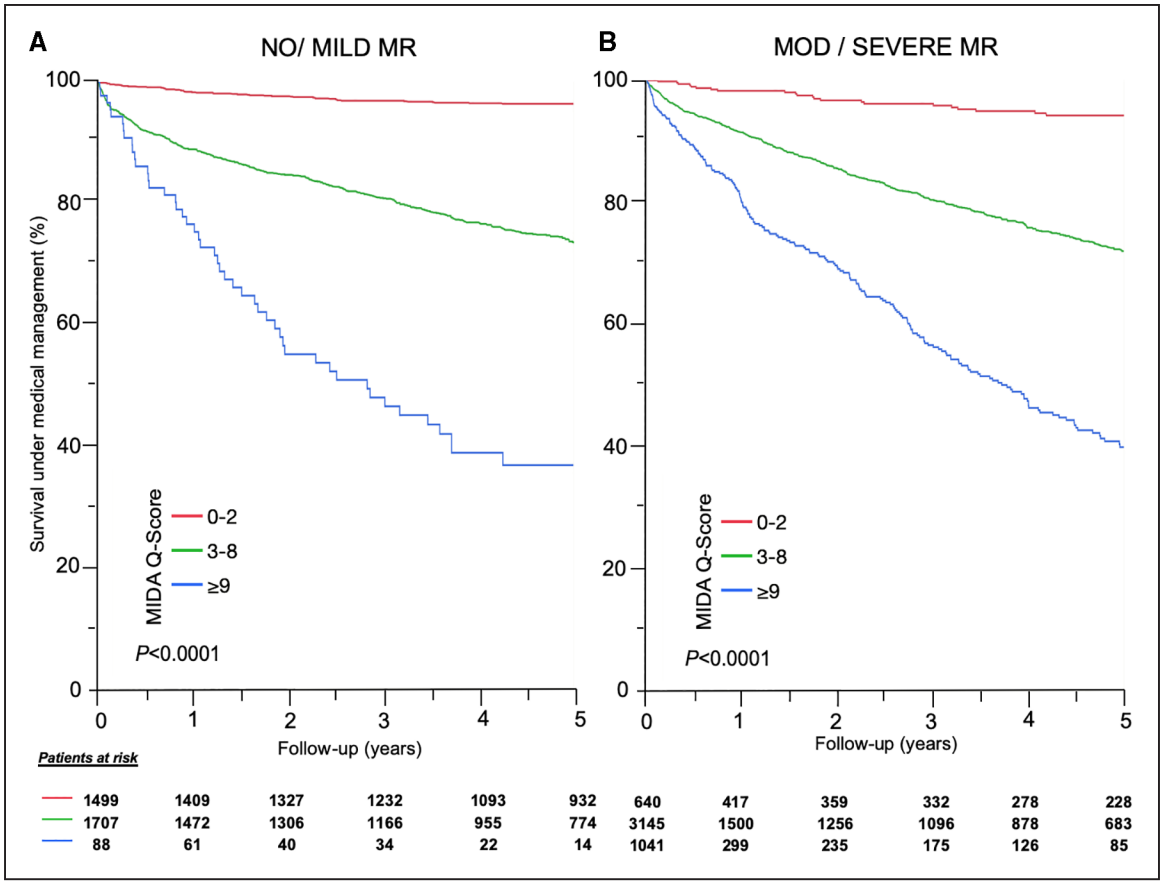

Figure 4. Survival associated with MIDA-Q score stratified by MR severity.
Kaplan-Meier survival curves for the range of MIDA-Q scores in patients with no/mild (**A**) and moderate/severe MR (**B**). In both subgroups, increasing MIDA-Q score is associated with excess long-term mortality. MIDA-Q indicates Mitral Regurgitation International Database Quantitative; and MR, mitral regurgitation.

with or without mitral annular disjunction,[25] and without or with DMR that may be of a considerable range of severity.[12] This is not the only form of MVP heterogeneity, because the response to MVP, that is, the cardiac consequences in terms of function, size, rhythm, hemodynamics, are also profoundly variable between patients,[26,27] affecting the clinical outcome of patient carriers of MVP with great heterogeneity. For the clinician, this combined heterogeneity of the disease nature and of its consequences make the risk assessment and clinical management profoundly complex. Thus, it may not be surprising that patients with MVP who represent the majority of organic mitral regurgitation in the developed countries remain profoundly undertreated worldwide and affected by serious excess mortality.[3,28,29]

Therefore, it is essential to integrate the various risk markers into a single instrument that also takes into account the specific DMR degree and to examine whether such an instrument can provide independent, strong, and incremental prediction of survival applicable to the entire spectrum of MVP and to a large geographical spectrum, in routine clinical practice. The integration of DMR severity was based on the fact that quantitative methods,[13] even applied in routine practice,[12] provide incremental prognostic information over qualitative grading, with ERO as the most powerful measure linked to outcome. On the basis of these quantitative principles and approach of integration with established prognostic measures, the MIDA-Q score verifies the present study hypothesis, crucially in the context of multiple institutions contributing their consecutive experience in routine clinical practice. In that regard, the observation that MIDA-Q score equally predicts MVP survival in the United States and Europe/Middle East is reassuring. Also, MIDA-Q is not just reflective of patients with the most severe DMR but performs equally well in patients labeled with no/mild DMR or any specific patient subset or any MVP characteristic. Thus, despite the wide heterogeneity of MVP in all its aspects, from genetics to anatomy to DMR severity to cardiac remodeling consequences, it is possible to integrate prognostic assessment into one single score that is associated between its extremes with a 5-year mortality ranging from 3% to 95%. Thus, in our opinion, it is essential to assign risk scores to patients with MVP by using the MIDA-Q score at diagnosis and also during follow-up of this progressive lesion that may cause progressive DMR.[4–6]

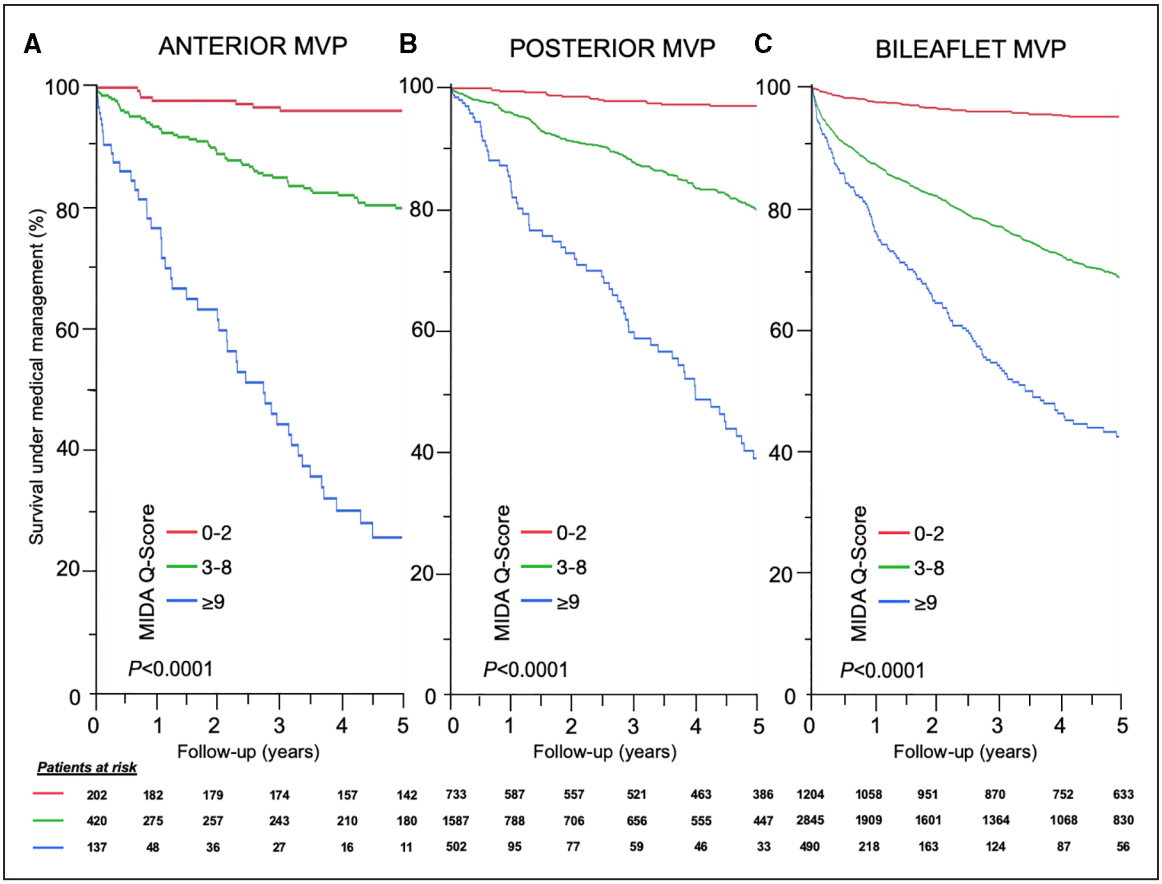

Figure 5. Survival associated with MIDA-Q score stratified by MVP anatomy.
Kaplan-Meier survival curves for the range of MIDA-Q scores in patients with anterior (**A**), posterior (**B**), and bileaflet (**C**) MVP. In all subgroups, increasing MIDA-Q score is associated with excess long-term mortality. MIDA-Q indicates Mitral Regurgitation International Database Quantitative; and MVP, mitral valve prolapse.

MVP Complex Management

MVP management has focused until recently on severe DMR, justifying aggressive valve repair, whereas patients with a lesser degree of DMR were considered benign, warranting no specific intervention even in the most recent version of clinical guidelines.[7,8] However, recent data have suggested that management presents more complexity with issues that involve the entire MVP spectrum and may require new clinical trials. For example, patients with MVP and notable DMR in the community incur profound undertreatment and excess mortality versus the general population.[3] It is remarkable that the cases that appear to be the simplest for decision making, ie, severe regurgitations with symptoms/class I indications for surgery, nevertheless experience profound undertreatment.[30,31] Although specific reasons for DMR undertreatment remain poorly defined, one possible explanation is linked to aging associated with MVP and the notable operative risk incurred by these patients that may discourage referral. Poor definition of the risk incurred under medical management may render evaluating the balance of surgical versus medical risk difficult. In this context, the considerable discriminating power of MIDA-Q score demonstrated by our study may play an important role in balancing the risks incurred and in supporting prompt referral of such patients to heart valve centers. Another section of the MVP spectrum regards patients with moderate DMR who nevertheless incur excess mortality versus the general population.[12] These patients are not part of the surgical interventions recommended by guidelines.[7,8] Whether surgical or new interventional valve repair (for high-risk patients particularly) will provide outcome improvement for these patients will require conducting clinical trials, for which MIDA-Q score selection of patients with notable risk under medical management may represent an important step in designing those trials. Another challenging MVP subset is that affected by the risk of serious ventricular arrhythmias, emphasized in recent outcome studies.[15,32] Neither the indications/modalities of risk monitoring nor the indications/modalities of rhythm therapies are well defined. Determining fruitful targets for rhythm monitoring/therapy will require clarification by cohort studies, clinical trials, or both, for which the MIDA-Q score, by providing a strong and independent risk assessment instrument, will be crucial to design such studies. Hence, recent data have clearly

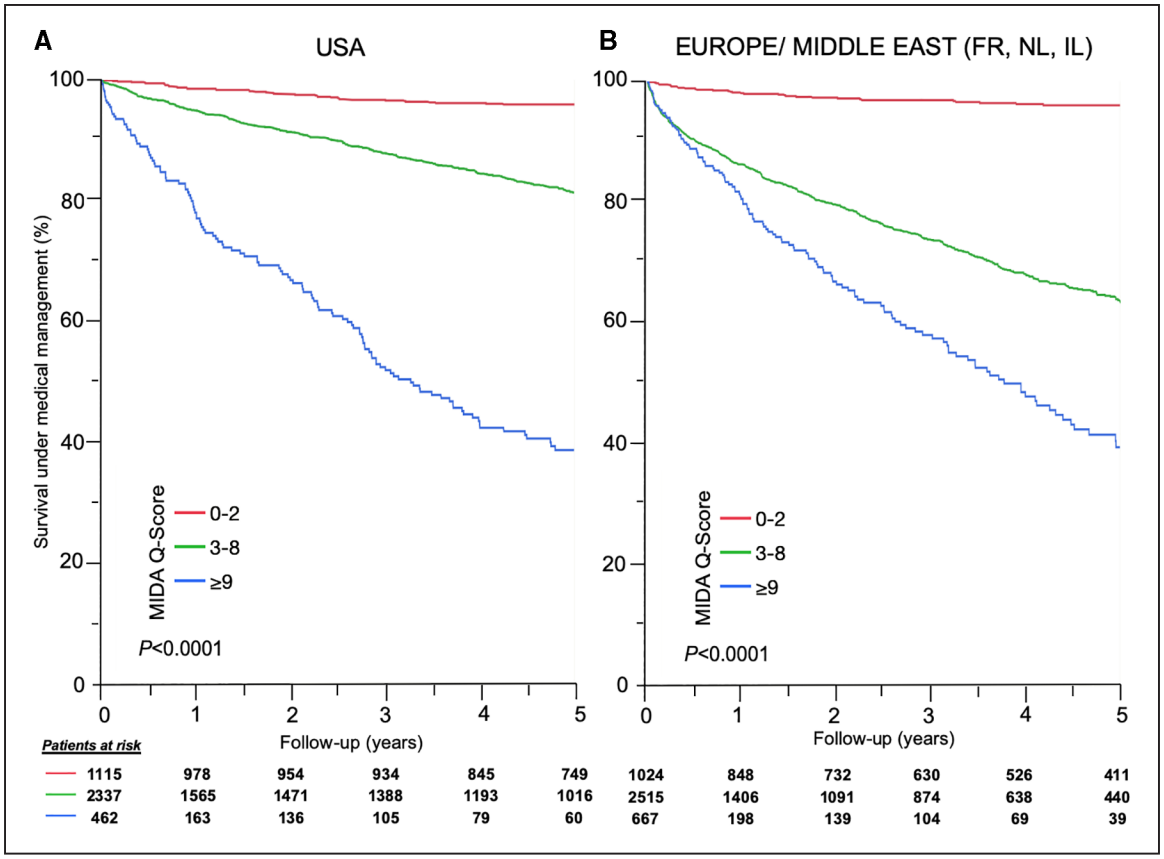

Figure 6. Survival associated with MIDA-Q score stratified by geographic origin.
Kaplan-Meier survival curves for the range of MIDA-Q scores in US (**A**) and European/Middle Eastern (**B**) patients. In both subgroups, increasing MIDA-Q score is associated with excess long-term mortality. FR indicates France; IL, Israel; MIDA-Q, Mitral Regurgitation International Database Quantitative; and NL, The Netherlands.

demonstrated that the risks attached to MVP are not confined to a single subset but involve the entire MVP spectrum, and, although the whole range of the potential therapeutic armamentarium has not been fully investigated to define therapeutic benefits, it is essential to proceed with comprehensive risk evaluations. In resolving these gaps of knowledge, even though a therapeutic path for every single risk subset cannot yet be defined, mortality risk assessment is indispensable, and we believe that the powerful results provided by our large cohort in routine practice place the MIDA-Q score as a central instrument for the necessary refinement of the complex clinical management of patients with MVP.

Study Strengths and Limitations

Cohort identification may be prospective, allowing prospective echocardiographic recordings adjudication by a core laboratory for uniformity, but it is plagued by low recruitment/power and limited applicability of measurements to routine clinical practice. The present cohort was identified retrospectively in each center out of unique laboratory repositories, but all measurements were performed prospectively by multiple operators and collected electronically without alteration, allowing us to coalesce a large and unique international cohort of consecutive isolated MVP with considerable strength provided by prospective DMR quantitation in routine practice. Thereby, results have wide applicability to routine practice and to broad distributions of all-comers diagnosed with MVP. Although it may be of interest to include not just academic routine practices, but also nonacademic private practices, current data acquisition/storage and integrity cannot yet be ascertained. Although epidemiological representation of all MVPs in all states/countries of geographical regions involved would be of interest, such endeavor is not possible. However, the MIDA-Q European cohort displays baseline characteristics remarkably similar to those of the EuroHeart survey for severe primary mitral regurgitation[29] (age 66 versus 67 years, female sex 46% versus 47.6%, creatinine clearance 66 versus 72 mL·min^{-1}·1.73 m^{-2}, or diabetes 11% versus 12.9%), highly suggestive that the MIDA-Q cohort, although not exhaustively enrolling throughout whole continents, has strong representativity of ESC constituencies. Because of legal restrictions to death certificates and the vagaries of coding death causes, outcome end points could not be provided for cardiac mortality, but instead we focused on the most

robust end point of overall mortality. Years of diagnostic enrollment (2003–2020) were adapted to correspond to implementation of mitral regurgitation quantitation (in routine practice and electronically retrievable) in each laboratory, but did not determine mortality (adjusted P=0.11). Missing values are intrinsic to any large-scale data obtained in routine practice. Patients with missing/impossible measurements were thus categorized as not having the positive finding of an abnormal characteristic for score calculation. However, to verify that this clinically sound approach does not affect results, as noted in the Results, we also conducted multiple imputations to account for missing variables, followed by bootstrapping analysis. This additional analysis demonstrated unaffected, strong, and independent association of MIDA-Q with excess mortality, with adjusted hazard ratio, 1.16 [1.15–1.18], per 1 score increment, P<0.0001, reinforcing the crucial importance of MIDA-Q score for MVP risk assessment. We used original MIDA score points unchanged in the MIDA-Q calculation for consistency, but the adjusted hazard ratios attached to each variable are remarkably consistent between these different cohorts (Table S1). Because it does not aim at predicting mortality attributable to comorbid conditions, MIDA-Q score discrimination power is expectedly incomplete (Harell C 0.665), whereas, in terms of cardiac markers, it is significantly improved over MIDA score alone.

Other predictors of mortality in DMR (eg, B-type natriuretic peptide,[33] strain,[34] MRI fibrosis)[35] will require prospective acquisition in cohorts of large magnitude for analysis of incremental prognostic power first, but may be added to MIDA-Q score in the future (if implemented in routine practice). Indeed, markers of surgical outcome (eg, Society of Thoracic Surgeons score, EuroScore)[21,36] have evolved over time to respond to new data, and this ongoing process of living instruments is applicable to the MIDA-Q score. Whether genetics will play a role in the risk scoring of patients with MVP remains uncertain, but some genes associated with the MVP phenotype may be causal to rapid progression or to poor myocardial response to MVP and DMR,[23] emphasizing the importance to uncover the link genetics-outcome in the future.

CONCLUSIONS

The present study demonstrates in a large international cohort focusing on isolated MVP, examined in routine practice with prospective quantitative DMR assessment, that the MIDA-Q score is strongly, independently, and incrementally associated with long-term survival under medical management. The link of MIDA-Q score to mortality remains independent in all subsets, including those with low or higher surgical risk, various DMR grades, geographical origin, or type of MVP. Hence, MIDA-Q score as a marker of outcome is immediately and widely usable in routine practice, to all forms of MVP and over its entire spectrum, to guide the clinical decision-making process and ultimately reduce DMR undertreatment.

ARTICLE INFORMATION

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Supplemental Material

Tables S1 and S2

Figures S1–S6

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