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The Mitral INsufficiency Echocardiographic score: A severity classification of myxomatous mitral valve disease in dogs

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Abstract

Background: There is no commonly shared severity score for myxomatous mitral valve disease (MMVD) based on routinely acquired echocardiographic variables.

Hypothesis/Objectives: To propose an easy-to-use echocardiographic classification of severity of MMVD in dogs.

Animals: Five hundred and sixty dogs with MMVD.

Methods: This was a retrospective, multicenter, observational study. The proposed Mitral INsufficiency Echocardiographic (MINE) score was based on 4 echocardiographic variables: left atrium-to-aorta ratio, left ventricular end-diastolic diameter normalized for body weight, fractional shortening, and E-wave transmitral peak velocity. Specific echocardiographic cutoffs were defined based on previous prognostic studies on MMVD, and severity scores were assigned as follows: mild (score: 4-5), moderate (score: 6-7), severe (score: 8-12), late stage (score: 13-14).

Results: Median survival time was significantly different ($P < .05$) between the proposed severity classes: mild (2344 days, 95% confidence interval [CI] 1877-2810 days), moderate (1882 days, 95% CI 1341-2434 days), severe (623 days, 95% CI 432-710 days), and late stage (157 days, 95% CI 53-257 days). A MINE score >8 was predictive of cardiac death (area under the curve = 0.85; $P < .0001$; sensitivity 87%, specificity 73%). In the multivariable analysis, all the echocardiographic variables of the MINE score were independent predictors of death because of heart disease ($P < .001$).

Conclusions and Clinical Importance: The MINE score is a new easy-to-use echocardiographic classification of severity of MMVD, which has been proven to be clinically effective as it is associated with survival. This classification provides prognostic information and could be useful for an objective echocardiographic assessment of MMVD.

KEYWORDS
cardiac death, heart failure, mitral regurgitation, prognosis, survival

Abbreviations: CHF, congestive heart failure; CI, confidence interval; E-vel, E-wave transmitral peak velocity; FS, fractional shortening; HR, hazard ratio; LA/Ao, left atrium-to-aorta ratio; LVIDDn, left ventricular end-diastolic diameter normalized for body weight; MINE, Mitral INsufficiency Echocardiographic; MMVD, myxomatous mitral valve disease.

1 | INTRODUCTION

Mitral insufficiency because of myxomatous mitral valve disease (MMVD) is the most common acquired cardiac disease in dogs, accounting for approximately 75% of cases of heart disease in dogs.[1] The American College of Veterinary Internal Medicine (ACVIM) guidelines are commonly used for the clinical classification of dogs with MMVD.[2] However, the echocardiographic assessment of MMVD plays a pivotal role in understanding the clinical and hemodynamic status, predicting congestive heart failure (CHF), deciding when to start treatment, assessing treatment effectiveness, and evaluating prognostic factors.[3-10]

Similarly to human medicine,[11,12] the echocardiographic evaluation of severity of MMVD in dogs is based on cardiac remodeling (left side atrioventricular enlargement), quantification of mitral regurgitation (size of the regurgitation jet by color-Doppler, effective regurgitant orifice area, proximal isovelocity surface area, vena contracta, and regurgitant fraction), and estimation of left ventricular filling pressure (mitral inflow, isovolumetric relaxation time, pulmonary venous flow, regurgitant jet profile, and tissue Doppler echo variables).[5,6,8,13-17] However, many of these methods are time-consuming and require multiple measurements. In addition, the evaluation of the variables is subject to both method and operator-dependent errors (intraobserver and interobserver variability) and requires the skills of a well-trained operator. In veterinary medicine, there is a lack of a commonly shared easy-to-use severity score for MMVD based on routinely acquired echocardiographic variables with low measurement variability. Such a score could help to objectively evaluate dogs with MMVD, with possible implications in the clinical and therapeutic management of the disease.

The aim of this study was thus to propose a Mitral INsufficiency Echocardiographic (MINE) score, as an easy-to-use echocardiographic classification of severity of MMVD based on routinely acquired echocardiographic variables. The hypothesis was that the MINE score is clinically effective since it is associated with median survival time of dogs with MMVD.

2 | MATERIALS AND METHODS

This was a retrospective, multicenter, and observational study. Dogs were recruited at the Anicura Istituto Veterinario Novara and the Department of Veterinary Sciences of the University of Pisa. Because of the retrospective study design, no institutional animal care and use approval or client consent were sought.

2.1 | Animals

Clinical databases of the Anicura Istituto Veterinario and the Veterinary Teaching Hospital of the University of Pisa were reviewed for dogs with an echocardiographic diagnosis of MMVD evaluated between 2011 and 2019. All dogs had to have undergone complete physical examination, chest radiographs, and echocardiography. Data regarding breed, sex, age, body weight, ACVIM stage, echocardiographic variables, and baseline treatment were obtained from case records. Clinical ACVIM classification was verified and updated, when needed, to the most recent guidelines.[2]

To be included in the study, all dogs had to have been available for an updated follow-up in December 2019 conducted via telephone interviews with owners and referring veterinarians. Dogs aged less than 3 years old, weighing more than 20 kg, having a fractional shortening of less than 25%, presenting atrial fibrillation, and being pregnant, or with other concomitant systemic or cardiac disease were excluded for the study.

2.2 | Echocardiographic examination and scoring system

Transthoracic echocardiographic examinations had been carried out by a board-certified cardiologist or by supervised residents in cardiology with ultrasound machines equipped with phased-array transducers and a simultaneous single-lead electrocardiogram. Dogs were imaged from right and left parasternal positions, and standard echocardiographic 2-dimensional, M-mode, and Doppler images were acquired without sedation.[18]

The proposed MINE score was based on 4 echocardiographic variables: (a) the left atrium-to-aorta ratio (LA/Ao), obtained from the right parasternal short-axis view[19]; (b) the left ventricular end-diastolic diameter normalized for body weight (LVIDDn), measured on the M-mode obtained from the right parasternal short-axis view[20]; (c) the left ventricular fractional shortening (FS), measured on the M-mode obtained from the right parasternal short-axis view[20]; and (d) the E-wave transmitral peak velocity (E-vel), obtained with the pulsed-wave Doppler from the left apical 4-chamber view.[5]

Based on the previous echocardiographic studies on severity and prognosis in dogs with MMVD,[3-5,8,9,14,16,21-23] specific severity cutoffs and relative scores were established for each of the above echocardiographic variables (Table 1). Based on the authors' clinical experience, a scoring system was arbitrarily created, and 4 severity classes were defined. The severity class was assigned based on the total score obtained from the summation of the single scores attained by each of the 4 echocardiographic variables (Table 2).

2.3 | Survival

Long-term outcome and survival were assessed by reviewing clinical databases and by telephone interviews with the owners or the referring vets. Cause of death was recorded. Death was divided into cardiac-related cause and noncardiac-related cause. Cardiac death was defined as death secondary to cardiogenic pulmonary edema or euthanasia because of refractory CHF. All dogs that died unexpectedly with no other apparent cause for death were assumed to have experienced sudden cardiac death and considered as cardiac-related death.

The survival data were finally updated in December 2019, and the statistical analysis was based on this final update.

2.4 | Statistical analysis

Descriptive statistics were generated. The normality of data distribution was tested using the Shapiro-Wilk test. Parametric or nonparametric tests were used in accordance with the Gaussian distribution. For categorical variables, comparison between different stages of MMVD was performed with Fisher's exact tests. The clinical usefulness of the proposed MINE score was tested by evaluating the association with survival. Survival was analyzed using Kaplan-Meier curves and log-rank tests (considering both cardiac-related deaths and all-cause mortality). The receiver operating characteristic (ROC) curve analysis and the Youden index were used to define the best cutoff score to predict cardiac death. The multivariate Cox proportional hazards regression analysis was used to evaluate the echocardiographic independent predictors of cardiac death. Statistical analysis was performed with commercially available statistical software (Prism 5, GraphPad Software Inc., San Diego, California; SPSS, IBM, New York, New York). A value of $P < .05$ was considered statistically significant.

TABLE 1 Selected echocardiographic cutoffs and relative scores

	Score			
	1	2	3	4
LA/Ao	<1.70	1.70-1.90	1.91-2.50	>2.50
LVIDDn	<1.70	1.70-2.00	2.10-2.30	>2.30
FS (%)	<45	45-50	>50	
E-vel (m/s)	<1.20	1.20-1.50	>1.50	

Abbreviations: E-vel, E-wave transmitral peak velocity; FS, fractional shortening of the left ventricle; LA/Ao, left atrium-to-aorta ratio; LVIDDn, left ventricular end-diastolic diameter normalized for body weight; .

TABLE 2 Severity classification based on the total score obtained from the summation of the single scores obtained with Table 1

Severity classification	Total score
Mild	4-5
Moderate	6-7
Severe	8-12
Late stage	13-14

3 | RESULTS

A total of 560 dogs with MMVD were included, with 242 females and 318 males, with a mean age of 10.7 ± 3.0 years (range 3-18 years) and a mean body weight of 8.7 ± 4.4 kg (range 1.5-20 kg). Most dogs were mixed-breed (n = 196), followed by Cavalier King Charles Spaniel (n = 69), Chihuahua (n = 47), Poodle (n = 34), Dachshund (n = 33), Yorkshire Terrier (n = 23), Jack Russel Terrier (n = 22), Pomeranian (n = 20), Pinscher (n = 18), Maltese (n = 18), Cocker Spaniel (n = 12), Epagneul Breton (n = 10), Shih Tzu (n = 9), and the remaining 49 dogs were of 22 other breeds. According to the ACVIM classification, 288 dogs were in stage B1, 110 dogs in stage B2, and 162 were in stage ACVIM C-D. Regarding treatment at inclusion, of those dogs in stage B1, 269 (93%) were not administered drugs, 13 (5%) were being treated with pimobendan, 6 (2%) an angiotensin converting enzyme inhibitor, and 2 (1%) spironolactone. In stage B2, 29 (26%) dogs were not administered drugs, 78 (71%) were being treated with pimobendan, 15 (14%) with an angiotensin converting enzyme inhibitor, and 7 (6%) with spironolactone. In stage C-D, 162 (100%) dogs were being treated with pimobendan, 155 (96%) an angiotensin converting enzyme inhibitor, 138 (85%) furosemide, 108 (67%) spironolactone, 24 (15%) torasemide, 7 (4%) sildenafil, 5 (3%) amlodipine, and 4 (3%) hydrochlorothiazide.

TABLE 3 Baseline clinical and echocardiographic data of all study dogs (n = 560) according to the severity class of the Mitral INsufficiency Echocardiographic (MINE) score

	Severity class			
	Mild (n = 239)	Moderate (n = 113)	Severe (n = 186)	Late stage (n = 22)
Sex (M/F)	125/114	71/42[a]	110/76	12/10
Age (years)	9.9 ± 3.2	10.8 ± 2.9[a]	11.6 ± 2.7[a]	11.2 ± 1.6[a]
Body weight (kg)	9.1 (1.5-20)	8.0 (2.1-19.8)	7.0 (1.5-20)[a]	5.8 (3.4-17.5)[a]
LA/Ao	1.5 (1.1-1.9)	1.7 (1.2-2.3)[a]	2.2 (1.7-3.5)[a,b]	2.9 (2.3-4.2)[a-c]
LVIDDn	1.5 (1.1-1.9)	1.7 (1.2-2.1)[a]	2.0 (1.4-3.1)[a,b]	2.3 (2.1-3.1)[a-c]
FS (%)	39 (27-50)	46 (29-77)[a]	50 (30-79)[a,b]	51 (46-62)[a,b]
E-Vel (m/s)	0.7 (0.4-1.2)	0.9 (0.5-1.4)[a]	1.3 (0.7-2.4)[a,b]	1.7 (1.3-2.6)[a-c]

Note: Data represent mean ± SD, median (min-max) or number (percentage).
Abbreviations: BW, body weight; E-vel, E-wave transmitral peak velocity; FS, fractional shortening of the left ventricle; LA/Ao, left atrium-to-aorta ratio; LVIDDn, left ventricular end-diastolic diameter normalized for body weight.
[a] $P < .05$ compared to mild cases.
[b] $P < .05$ compared to moderate cases.
[c] $P < .05$ compared to severe cases.

At the end of the study, 325 (58%) dogs were still alive and 235 (42%) dogs had died, of which 147 (63%) dogs had a cardiac-related death and the remaining 88 (37%) dogs died due to noncardiac-related reasons. Cardiac death was due to cardiac-related euthanasia in 69 dogs (47%), cardiogenic pulmonary edema in 46 dogs (31%), and sudden death in 32 dogs (22%).

According to the proposed MINE score, 239 (43%) dogs were classified as mild, 113 (20%) as moderate, 186 (33%) as severe, and 22 (4%) as late stage (Table 3). Considering cardiac death, the median survival time was significantly different between all the proposed severity classes: 2344 days for mild cases (95% confidence interval [CI] 1877-2810 days), 1882 days (95% CI 1341-2434 days) for moderate cases, 623 days for severe cases (95% CI 432-710 days), and 157 days for late-stage cases (95% CI 53-257 days) (Figure 1). Significant differences between all the proposed severity classes were present also considering all-cause mortality (Figure 2). According to the ROC curve analysis and the Youden index, the best cutoff predictive of cardiac-related death was a total score >8 (area under the curve = 0.85, 95% CI 0.81-0.89; $P < .0001$; sensitivity 87%, 95% CI 82%-90%; specificity 73%, 95% CI 65%-80%).

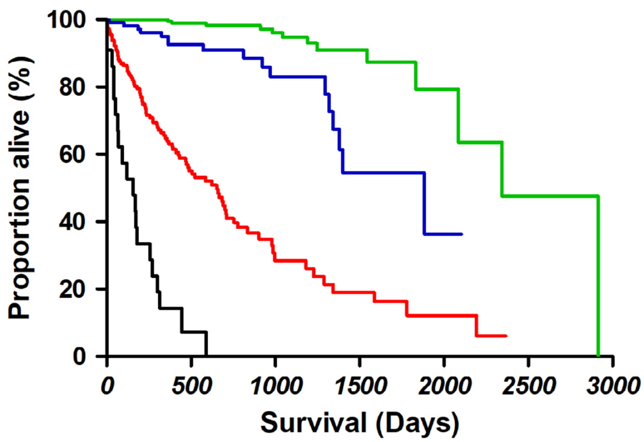

FIGURE 1 Kaplan-Meier curves illustrating survival time from initial diagnosis to cardiac-related death for each Mitral INsufficiency Echocardiographic (MINE) score severity class, mild (green line), moderate (blue line), severe (red line) and late-stage (black line). $P < .0001$

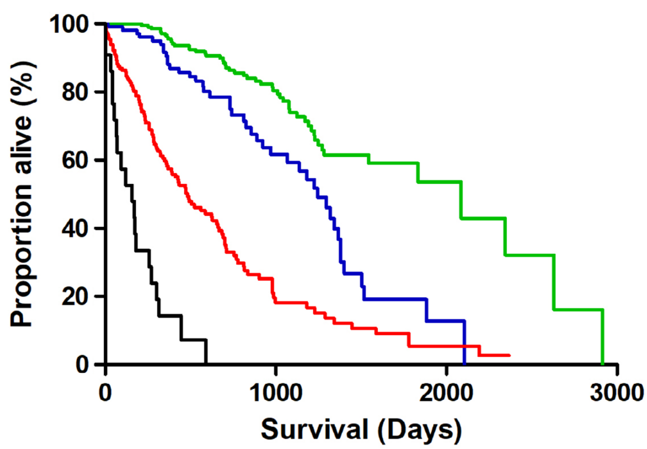

FIGURE 2 Kaplan-Meier curves illustrating survival time according to the Mitral INsufficiency Echocardiographic (MINE) score severity class when all causes of death were considered. Severity classes: mild (green line), moderate (blue line), severe (red line) and late-stage (black line). $P < .0001$

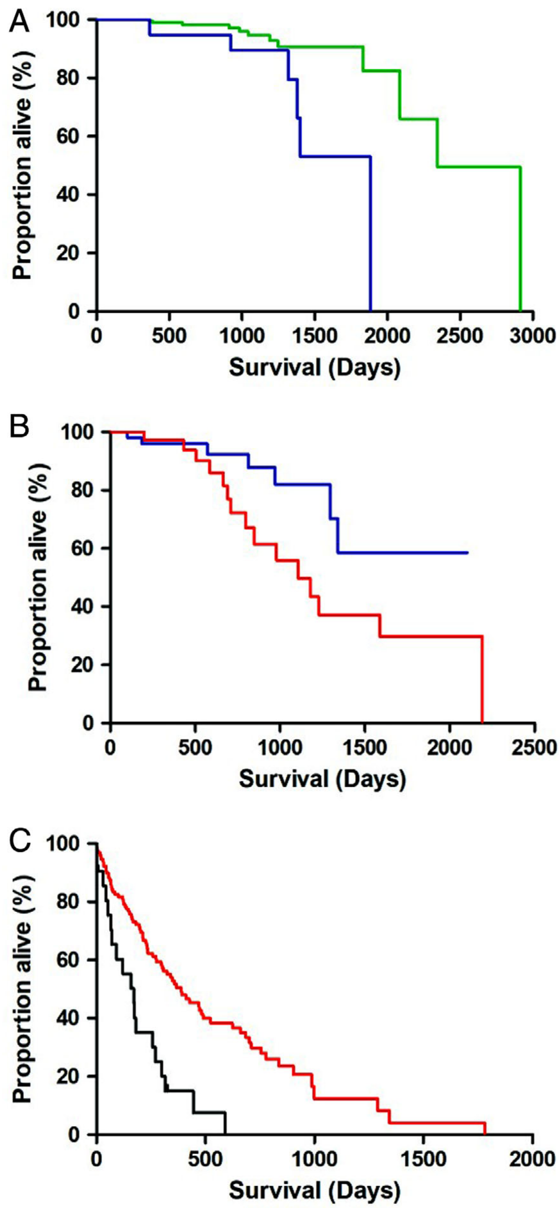

FIGURE 3 Kaplan-Meier curves illustrating survival time from initial diagnosis to cardiac-related death for each ACVIM stage subdivided according to the Mitral INsufficiency Echocardiographic (MINE) score severity class. A, ACVIM stage B1, with mild cases (green line) versus moderate cases (blue line) ($P = .003$). B, ACVIM stage B2, with moderate cases (blue line) versus severe cases (red line) ($P = .041$). C, ACVIM stage C-D, with severe cases (red line) versus late-stage cases (black line) ($P < .0001$)

Considering the ACVIM stage, dogs were subdivided according to the MINE score severity class. Of those dogs in stage B1, 231 were classified as mild, 51 as moderate, and 6 as severe. In stage B2, 8 were classified as mild, 57 moderate, 45 severe. In stage C-D, 7 were moderate, 134 severe, and 21 late stage. Differences in survival according to the MINE score severity class were evaluated between groups including at least 20 dogs (Figure 3). Of those in stage B1, mild cases had a significantly longer survival time (2344 days; 95% CI 1879-2808 days) than moderate cases (1882 days; 95% CI 1348-2416 days; $P = .003$). In stage B2, moderate cases had a significantly longer survival time (1644 days; 95% CI 1371-1784 days) than severe cases (1107 days; 95% CI 799-2192 days; $P = .04$). In stage C-D, severe cases had a significantly longer survival time (388 days; 95% CI 264-469 days) than late-stage cases (171 days; 95% CI 93-249 days; $P < .0001$).

In the multivariate analysis, all the selected variables included in the MINE score were independent predictors of cardiac death as follows: LA/Ao (hazard ratio [HR] = 2.05; 95% CI 1.27-3.29; $P = .003$); LVIDDn (HR 2.72; 95% CI 1.32-5.63; $P = .007$); FS% (HR = 1.03; 95% CI 1.01-1.05; $P = .006$) and E-vel (HR = 5.63; 95% CI 3.05-10.38; $P < .0001$).

4 | DISCUSSION

Our MINE score originated from the idea of selecting core echocardiographic variables for the classification of severity of mitral insufficiency in dogs with MMVD. Four basic echocardiographic variables were selected for the assessment of left cardiac remodeling (LA/Ao and LVIDDn), left ventricular dynamics (FS), and left ventricular filling pressure (E-vel). These variables were chosen because they are routinely acquired for the clinical management of dogs with MMVD and because of their good intraoperator and interoperator variability (<5%-10%).[5,24-28] In addition all the echocardiographic variables included in the MINE score are of prognostic significance in dogs with MMVD.[3-5,8-10,14,16,21-23,29]

Based on our results, the severity of mitral insufficiency assessed with the MINE score is associated with survival time and the proposed score is predictive of cardiac death. The significance of the MINE score classes was maintained also considering all-cause mortality; in fact the majority of the dogs in the study had died of cardiac-related causes. In addition, the severity of MMVD is a relevant comorbidity that might have affected the prognosis of other concomitant diseases, since it is a possible fatal surrogate for a noncardiac disease. For these reasons, the MINE score can provide a useful prognostic role in the management of dogs with MMVD. This score could also be used as an easy-to-use tool for the standardization of the echocardiographic assessment of severity of MMVD in dogs, which would also be useful for both clinical management of the disease and for research purposes.

In human medicine, there are well-established, commonly shared echocardiographic classifications of severity of mitral insufficiency.[11,12] These classifications include the evaluation of structural features (mitral valve morphology, left cardiac remodeling), as well as the Doppler qualitative assessment (color flow jet area, flow convergence zone, density, and profile of mitral regurgitation jet), semiqualitative assessment (vena contracta width, pulmonary vein flow, mitral inflow), and quantitative assessment of mitral regurgitation (effective regurgitant orifice area, regurgitant volume, and regurgitant fraction).

Although most of these echocardiographic variables have been studied in veterinary medicine, many of these methods are time-consuming, involve multiple measurements, and require the skill of a well-trained operator because meticulous image acquisition is essential to obtain repeatable results, otherwise measurement variability and interobserver reproducibility can be poor.[14-16,30-32] Color flow imaging of the mitral regurgitation jet area is the most common way to assess mitral regurgitation severity in dogs. However, this method is not considered reliable to quantify the severity of mitral insufficiency in humans.[11,12] In dogs, the apparent simplicity of the jet area method may be why it is often used as a measure of mitral insufficiency severity. However, the correlation of jet area with mitral regurgitation severity and its reproducibility have been reported as poor.[8,31] Among the semiqualitative methods, the vena contracta width is a measure of the effective regurgitant orifice. Compared to many qualitative methods, this works equally well for central and eccentric jets. However, it is dependent on orifice geometry and is not reliable in multiple jets.[12] One study in dogs with MMVD reported that the vena contracta and E-vel correlated strongly with cardiac magnetic resonance imaging-derived mitral regurgitant fraction; however, E-vel had superior repeatability and was measured in all dogs.[31] Among the quantitative methods, the evaluation of the proximal isovelocity surface area is one of the most commonly used methods for the assessment of the effective regurgitant orifice area and the regurgitant volume. However, it is not reliable in eccentric jets. Moreover, small errors in radius measurement can lead to substantial errors (10%-25%) in the effective regurgitant orifice area due to the squaring of errors.[12,33] In addition, the echocardiographic existence of the dynamic behavior and variability of mitral regurgitation has been described in dogs with mitral valve prolapse, which should be considered as a limitation inherent to the proximal isovelocity surface area method.[34] Real-time 3-dimensional echocardiography was reported as an effective tool to assess the effective regurgitant orifice area in dogs with MMVD[32,35]; however, the need for experienced operators in 3-dimensional echocardiography and the cost of the technology limit its use in clinical practice. Lastly, other spectral Doppler-based quantitative methods for the assessment of the effective regurgitant orifice area and regurgitant volume (eg, the mitral inflow and stroke volume method) are considered to be time-consuming, with several drawbacks and are not recommended as a first-line method to quantify mitral regurgitation severity in humans.[11,12]

Based on all this evidence, we propose the MINE score. It is based on easy-to-acquire echocardiographic variables, with good repeatability, that are associated with survival in dogs with MMVD. This is because more complicated variables can lead to a high degree of interobserver variability which can adversely influence clinical decision making. Hence, a simple yet accurate reproducible and clinically applicable guide is needed to identify and follow-up dogs with

MMVD. There are other proposals of mitral regurgitation severity scores[32,36,37] based on mitral valve leaflet anatomy, left atrial size, left ventricular size, color Doppler regurgitant jet area, mitral inflow (E wave velocity and deceleration time), and continuous wave Doppler regurgitant jet density. However, many of these variables are based on a subjective assessment and the association of these scores with survival time was not evaluated.

Dogs with MMVD are clinically classified according to the ACVIM guidelines, in which the LA/Ao and LVIDDn are used to define cardiac remodeling. However, no commonly shared guidelines are available in veterinary medicine for the echocardiographic assessment of mitral regurgitation severity in dogs with MMVD. In our study, the proposed MINE score was matched with the ACVIM classification. This revealed significant differences in survival time for dogs belonging to the same ACVIM stage but presenting a different MINE score severity class. This could indicate the potential complementary utility of the MINE score in the clinical management of dogs affected by MMVD. According to the MINE score, most dogs in our study belonging to stage B1 showed a mild or moderate degree of mitral insufficiency. Most moderate cases had LA enlargement with normal LV size and showed a worse prognosis compared to mild cases. According to the current ACVIM guidelines,[2] asymptomatic dogs showing LA enlargement with normal LV dimension are classified as B1; those with both LA and LV enlargement are classified as B2. A minority of B1 cases (2%) in our study were classified as severe according to the MINE score because they all showed LA/Ao >1.9% and FS >50%, values that have been previously shown to be predictive of cardiac death in MMVD in dogs.[3,5,14,16,22] However, these cases were classified as B1 because they had a normal LV size. Based on these considerations, further studies on the prognosis of B1 cases with different degrees of cardiac remodeling may be useful. Regarding stage B2, according to the MINE score, most dogs showed a moderate or severe degree of mitral insufficiency. Severe cases showed a worse prognosis than moderate cases, with many dogs having relevant cardiac remodeling and echocardiographic signs of high LV filling pressures. Dogs in stage B2 represent a heterogeneous group of animals, with some individuals presenting a slow progression of the disease and others rapidly developing CHF.[9,10,38] The MINE score could be useful in identifying B2 dogs with higher risk of cardiac death. Lastly, a relevant number of dogs in stage C-D were classified as severe or late-stage according to the MINE score. The late-stage dogs had a substantially worse prognosis than the severe cases, with a median survival time of less than 6 months. Identification of late-stage cases may provide important prognostic information, indicate the need for more frequent cardiac follow-up, and help in the selection of those cases with a higher indication for cardiac surgery (eg, mitral valve repair).

Our study has some limitations. First, data regarding arterial blood pressure were not available in all dogs included in the study, thus systemic hypertension could have influenced the prognosis in some cases. However, systemic hypertension in dogs is usually secondary to relevant systemic diseases,[39] such as renal or endocrine diseases, which were considered among the exclusion criteria in our study. Second, the cases included in the study consist in a referral hospital sample, which might not accurately represent the general canine population. Third, all echocardiographic examinations were acquired by a board-certified cardiologist or by supervised cardiology residents. Thus, possible different results could originate from sonographers with less clinical experience and/or echocardiographic training. Lastly, because of the retrospective nature of the study, medical treatment was not homogenous in the study sample.

In conclusion, we have proposed the MINE score, which is an easy-to-use echocardiographic classification of severity of MMVD, proven to be clinically effective since it is associated with survival. This classification provides prognostic information and could be useful for an objective echocardiographic assessment of MMVD. The MINE score could also be useful in identifying asymptomatic dogs with higher risk of cardiac death.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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