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Research Article

Retrospective analysis of clinical and echocardiographic features in dogs with Myxomatous Mitral Valve Disease

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Abstract

Myxomatous mitral valve disease (MMVD) is a commonly recorded acquired valvular disease particularly affecting middle and old-aged dogs. This study aimed to provide a reference for clinical diagnosis and its progression evaluation. A total of 244 (n=244) dogs were categorized into three stages (B1, B2 and C) as per ACVIM classification based on clinical condition. The clinical and echocardiographic characteristics of MMVD in dogs from Shenzhen, China, were analyzed retrospectively by this study. Statistical analysis was performed to compare clinical and echocardiographic characteristics among different stages of dogs with MMVD. The breeds most commonly affected were Poodle (39.8%), Pomeranian (19.7%) and Bichon Frise (8.2%). No significant differences (P>0.05) in body weight were observed among the stages. Signs of wheezing, coughing and exercise intolerance were more pronounced in later stages (B2 and C) indicating a progression of the disease. Stage C dogs exhibited a higher prevalence of cyanosis, dyspnea, weakness, abdominal and pericardial effusions compared to stage B1 dogs. Cardiac remodeling could be predicted by age ≤9.5 and heart murmur ≥2.5, while congestive heart failure (CHF) in MMVD dogs with remodeling was predicted by a heart murmur ≤4.5 and a Mitral Insufficiency Echocardiographic (Mine) score ≥10.5. Examination of clinical characteristics including breed, age, murmur and symptoms of affected dogs combining with echocardiography may aid veterinarians in predicting CHF in clinical settings. The findings of this study can offer valuable insights into the clinical diagnosis and prognosis of MMVD.

Keywords: Clinical features, Dogs, Echocardiography, Myxomatous mitral valve disease

Highlights

- Poodle, Pomeranian and Bichon Frise are the top three breeds with MMVD prevalence rates
- As the condition of MMVD worsens, affected dogs gradually develop clinical signs such as wheezing, coughing, exercise intolerance, cyanosis of mucous membranes, fainting, dyspnoea, weakness, pleural effusion, abdominal effusion, pericardial effusion, etc
- Age 9.5 years and heart murmur grade 2.5 were the thresholds for dogs in stages B1 and B2, and heart murmur grade 4.5 and Mine score of 10.5 were the thresholds for dogs in stages B2 and C

INTRODUCTION

Canine degenerative valve disease (Myxomatous mitral valve disease, MMVD) is the most prevalent heart disease in middle-aged and elderly dogs (Borgarelli and Schoemen, 2012). It is reported that MMVD accounts for approximately 75% of canine heart diseases worldwide (Borgarelli and Schoemen 2012; Keene *et al.*, 2019). This condition is particularly prevalent in small and medium-sized dogs weighing less than 15 Kg and its incidence increases with age, with prevalence rates ranging from 30% to 70% in dogs over 10 years old and in some breeds the lifetime prevalence can reach 100% (Borgarelli and Schoemen, 2012). MMVD is characterized by the mitral valve undergoing mucopolysaccharides deposition with nodular distortion of leaflets, leading to the production of redundant valve tissue, valve prolapse and damage to multiple leaflet segments (Maréchaux *et al.*, 2017). The progression of mucopolysaccharides results in valve thickness, stiffening, deformation and calcium salt deposition, leading to insufficiency (Burchell and Shoeman, 2014). This damage causes abnormal leaflet closure during ventricular systole, leading to a portion of blood flow from the left ventricle (LV) being regurgitated back into the left atrium (LA), a condition known as Mitral Regurgitation (MR) (O'Brien *et al.*, 2021). The increased regurgitant flow leads to the dilation of the left atrium and left ventricle, manifesting

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as preload overload and triggering congestive heart failure (CHF) (Burchell and Shoeman, 2014; Keene *et al.*, 2019). Affected dogs exhibit a range of clinical symptoms, including shortness of breath, difficulty breathing, coughing, pulmonary edema, and exercise intolerance, significantly impacting their quality of life (Burchell and Shoeman, 2014).

MMVD can be detected through auscultation (systolic heart murmurs) (Serfass *et al.*, 2006) and echocardiography (valve prolapse and mitral regurgitation) (Borgarelli *et al.*, 2004). According to the American College of Veterinary Internal Medicine (ACVIM) Consensus Guidelines for MMVD, dogs with MMVD are classified into stages A (breed predisposition), B1 (subclinical and cardiac non-remodeling), B2 (subclinical and cardiac remodeling), C (CHF) and D (end-stage CHF) (Keene *et al.*, 2019). The hallmark of CHF in dogs with MMVD is the presence of pulmonary edema observed under direct examination (Ward *et al.*, 2018; Keene *et al.*, 2019). Numerous retrospective studies have provided evidence for predicting CHF in dogs with MMVD (Hansson *et al.*, 2002; Cornell *et al.*, 2004; Baron *et al.*, 2016; vanStaveren *et al.*, 2023). Some researchers have even proposed the Mitral Insufficiency Echocardiographic (Mine) scoring system to assess the severity of MMVD, categorizing dogs into mild (4-5 points), moderate (6-7 points), severe (8-12 points), and last stage (13-14 points) (Vezzosi *et al.*, 2021). This scoring system offers a more objective assessment of the prognosis of dogs with MMVD. However, there is a gap in the literature regarding the clinical and echocardiographic characteristics of dogs with MMVD without CHF and those with CHF under conditions of cardiac remodeling. Although some previous studies have shown that disease severity in dogs with MMVD correlates with the intensity of heart murmurs (Ljungvall *et al.*, 2014), still there is a lack of research on the critical value of heart murmurs. Therefore, the objectives of this study were to investigate the basic information and imaging characteristics of MMVD in dogs in the Shenzhen area from 2021 to 2023, to identify risk factors for CHF in dogs with MMVD under cardiac remodeling and to summarize the clinical characteristics and echocardiographic features of MMVD in each stage of ACVIM thereby providing a reference for the clinical diagnosis of MMVD in dogs.

MATERIALS AND METHODS

Study animals: The study population consisted of 244 dogs (n=244) diagnosed with MMVD, sourced from Ringpai Pet Hospital, including Fuhua Nanshan Hospital and Baijia Buji Hospital located in Shenzhen, Guangdong Province, China. The inclusion criteria for the study were as follows: 1) Absence of echocardiographic evidence of congenital heart disease including mitral valve dysplasia (Chetboul and Tissier, 2012; Sudunagunta *et al.*, 2021); 2) No echocardiographic evidence of dilated cardiomyopathy (DCM) in dogs, defined by a left ventricular fractional shortening (FS)<20% (Dukes-McEwan *et al.*, 2003); 3) Presence of echocardiographic evidence of mitral valve prolapse (MVP) or any degree of mitral leaflet thickening (Chetboul and Tissier, 2012); 4) MR identified on color Doppler echocardiography (Chetboul and Tissier, 2012); 5) Exclusion of dogs with MMVD and non-type II pulmonary hypertension; 6) No prior history of cardiac disease or other systemic disease.

The dogs with MMVD included in the survey were graded according to the consensus report of the ACVIM (Keene *et al.*, 2019): Stage B1: (i) MVP with mild MR was detected on echocardiography; (ii) there was no evidence of cardiac remodeling (Left ventricular end-diastolic diameter normalized for body weight [LVIDdn]<1.7; Left atrium-to-aorta ratio [LA/AO]<1.6); and (iii) the affected dogs did not have CHF (pulmonary oedema was not detected on thoracic digital radiography [DR]). Stage B2: (i) MVP with MR was detected on echocardiography; (ii) evidence of cardiac remodeling was detected (LVIDdn≥1.7; LA/AO≥1.6); and (iii) the affected dogs did not have CHF (pulmonary oedema was not detected on thoracic DR). Stage C: (i) MVP with MR was detected on echocardiography; (ii) evidence of cardiac remodeling was detected (LVIDdn≥1.7; LA/AO≥1.6); and (iii) the affected dogs developed CHF (pulmonary oedema was detected on thoracic DR).

Clinical data: Data collected from case records included age, sex, weight, breed, heart murmurs, presence or absence of pulmonary edema, presence or absence of cough, respiratory condition and exercise tolerance of dogs with MMVD. The presence of pulmonary edema was determined by thoracic DR (Ward *et al.*, 2018), while coughing was observed through clinical examination. Respiratory conditions were categorized as shortness of breath (at rest, respiratory rate>30 breaths/min) (Porciello *et al.*, 2016) and no shortness of breath; exercise tolerance was categorized as exercise intolerance and exercise tolerance; and the presence or absence of mucous membrane cyanosis, fainting, respiratory distress, weakness and accumulation of fluid in the body

cavities (including thoracic, abdominal and pericardial effusions) was also recorded. The intensity of the heart murmur was recorded as grades I to VI, graded as follows: "soft" (I/VI and II/VI), "moderate" (III/VI), "loud" (IV/VI), "thrilling" (V/VI and VI/VI) (Serfass *et al.*, 2006; Ljungvall *et al.*, 2014).

Echocardiographic data: Echocardiographic data included LA/AO, LVIDdn, FS and the E-wave transmitral peak velocity (E-Vel). Two-dimensional (2D) echocardiography was performed using a 3-8.5 MHz ultrasound machine. During the examination, all affected dogs were not sedated and were artificially restrained in the left lateral decubitus and right lateral decubitus positions for scanning while the echocardiogram was recorded. Morphology of valve thickening or MVP was assessed using 2D mode in right parasternal long axis four chamber views (Pedersen *et al.*, 1996). Mitral and tricuspid regurgitation were observed in the right parasternal five chamber and left apical four chamber viewswith the color Doppler mode switched on, and the maximum velocities of MR and TR were measured by the continuous Doppler method with the Nyquist velocity limits set at 0.6-0.7 m/sec (Yosefy *et al.*, 2009). In the right parasternal short axis aortic view, the diameters of the aorta and the LA were measured with 2D measurements in the last frame after aortic valve closure to obtain the LA/AO ratio (Hansson *et al.*, 2002). In the right long-axis four-chamber heart, the maximum LV internal diameter was measured at end-diastole in the M-mode, and LVIDdn was calculated by dividing the LV internal diameter by the formula 0.294 to the power of body weight (Cornell *et al.*, 2004). Similarly, in the right long-axis four-chambered heart, the maximum LV internal diameter and the minimum left ventricular internal diameters were measured at end-diastole and end-systole, respectively, using the M-mode to obtain the FS (Schober and Baade, 2000). The velocity of blood flow from the LA through the mitral valve to the LV was measured using pulsed Doppler in the left apical four-chamber heart to obtain E-Vel (Schober *et al.*, 2010). The aortic and pulmonary trunks were exposed in the image in the left apical five-chamber heart and the maximum flow velocities through the aortic valve and pulmonary valve were measured using PW while the maximum regurgitant velocities were recorded in the presence of aortic and pulmonary regurgitation (AR and PR) (Bussadori *et al.*, 2000). Finally the Mine score was obtained by combining the four indexes of LA/AO, LVIDdn, FS and E-Vel to obtain the severity score of MMVD in dogs. It was graded as follows: 4-5 as "Mild", 6-7 as "Moderate", 8-12 as "Severe", 13-14 as "Last stage" (Vezzosi *et al.*, 2021).

Statistical analysis: All data were analyzed using SPSS Statistics 26.0. Clinical characteristics (age, sex, weight, breed, heart murmur, clinical symptomatic condition) and echocardiographic data (LA/AO, LVIDdn, FS, E-Vel, Mine score, etc.) were imported, with the independent variables being the aforementioned data and the dependent variable being the stage of the study dogs (stage B1, stage B2, and stage C). All continuous variables were expressed as the median and interquartile range (IQR). Non-parametric tests were used to analyze the variability of the data. Categorical variables were analyzed for variability using chi-squared tests. Receiver Operating Characteristic (ROC) curve analysis and the Jordan index were used to determine the optimal threshold for predicting the onset of CHF in dogs with MMVD. P"ÿ0.05 was considered statistically significant.

RESULTS

Clinical characteristics: A total of 244 dogs (n=244) with MMVD were included in the study, with 156 being male (63.9%) and 88 female (36.1%). Based on the ACVIM classification, 170 dogs were categorized as stage B1, 46 in stage B2 and 28 in stage C. The most commonly affected breed was Poodles (97, 39.8%), followed by Pomeranians (48, 19.7%), Bichon Frises (20, 8.2%), Schnauzers (13, 5.3%), Chihuahuas (11, 4.5%), Papillons (5, 2%), Shih Tzus (5, 2%) with the remaining 45 dogs represented from 15 other breeds (Fig. 1). The body weight of the study dogs ranged

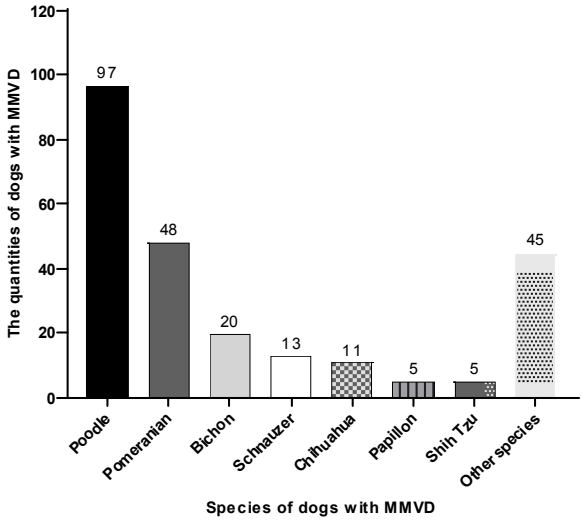

Fig. 1. Breed distribution of 244 dogs with MMVD

Fig. 2. Age distribution of 244 dogs with MMVD

Variables	Totally	B1	B2	C	χ^2	P
Quantities	244	170(69.7%)	46(18.9%)	28(11.5%)	-	-
Weight(kg)	5.1(3.6-7.0)	5.4(3.6-7.4)	5.0(3.8-6.0)	4.8(3.3-6.0)	-	0.397
Age(years)	10(7-12)	9(7-11)#^	11(9-13)*	12(10-13)*	-	<0.001
Wheezing	41(16.8%)	11(6.5%)#^	11(23.9%)*^	19(67.9%)*#	66.852	<0.001
Coughing	69(28.3%)	24(14.1%)#^	21(45.7%)*^	24(85.7%)*#	69.196	<0.001
Exercise intolerance	36(14.8%)	11(6.5%)#^	10(21.7%)*^	15(53.6%)*#	44.604	<0.001
Mucosal cyanosis	12(4.9%)	4(2.4%)^	2(4.3%)	6(21.4%)*	12.836	<0.01
Syncope	11(4.5%)	4(2.4%)	4(8.7%)	3(10.7%)	6.438	0.030
Dyspnea	9(3.7%)	2(1.2%)^	2(4.3%)	5(17.9%)*	13.226	<0.01
Weakness	7(2.9%)	2(1.2%)^	2(4.3%)	3(10.7%)*	7.204	0.014
Pleural effusion	1(0.4%)	0(0.0%)	1(2.2%)	0(0.0%)	3.864	0.303
Abdominal effusion	3(1.2%)	0(0.0%)^	1(2.2%)	2(7.1%)*	8.194	0.015
Pericardial effusion	2(0.8%)	0(0.0%)^	1(2.2%)	1(3.6%)*	5.422	0.091

*Statistically different compared to group B1. #Statistically different compared to group B2. ^Statistically different compared to group C.

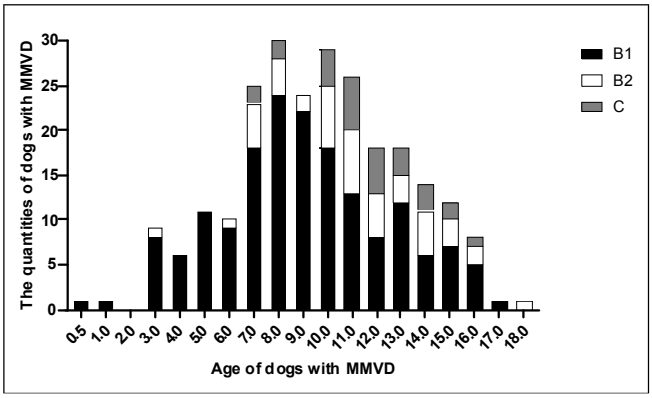

Fig. 2. Age distribution of 244 dogs with MMVD

from 1.49 to 40 kg, with a median of 5.1 kg (interquartile range (IQR): 3.6-7.0 kg). The median weight for stage B1 was 5.4 kg (IQR: 3.6-7.4 kg), for stage B2 was 5.0 kg (IQR: 3.8-6.0 kg), and for stage C was 4.8 kg (IQR: 3.3-6.0 kg). The non-parametric test indicated no significant difference in body weight among the three stages (P=0.397>0.05) (Table 1).

The age of the study dogs ranged from 6months to 18 years with a median of 10 years (IQR: 7-12 years). The median age for stage B1 was 9 years (IQR: 7-11 years), for stage B2 was 11 years (IQR: 9-13 years) and for stage C was 12 years (IQR: 10-13 years). The results of non-parametric tests showed significant differences (P<0.001) in age among the three stages, with significant differences between stage B1 and B2, and C (P<0.01), but no significant difference among B2 and C groups (P = 0.371) (Table 1). The ROC curve analysis indicated that age is significant factor in diagnosing the presence of cardiac remodeling in dogs with MMVD without heart failure (stages B1 and B2), and is a good indicator for diagnosing the presence of cardiac remodeling (AUC of 0.665, P<0.001) (Fig. 3-A). Age≥9.5 had 71.7% sensitivity and 58.8% specificity for predicting cardiac remodeling in dogs with MMVD without heart failure. In the context of cardiac remodeling, age was not significant in diagnosing the presence of heart failure in dogs with MMVD

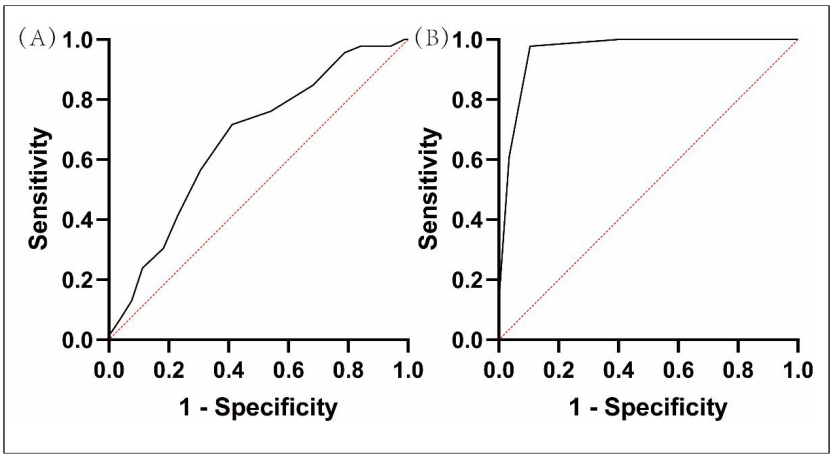

Fig. 3. In the absence of congestive heart failure, age and murmur intensity are effective predictors of cardiac remodeling. (A) The ROC curve for age in dogs from groups B1 and B2 illustrates its predictive capability. (B) The ROC curve for murmur intensity in dogs from groups B1 and B2 highlights its effectiveness as a predictor

(stages B2 and C) (AUC of 0.56, p=0.388).

Out of all the study dogs, 69 (28.3%) coughing, 41 (16.8%) exhibited wheezing, 36 (14.8%) exercise intolerance, 12 (4.9%) mucosal cyanosis, 11 (4.5%) syncope, 9 (3.7%) dyspnea, 7 (2.9%) weakness, 3 (1.2%) abdominal effusion, pericardial effusion in 2 dogs (0.8%), and pleural effusion in only one dog (0.4%). The symptoms in dogs with each stage are detailed (Table 1). Signs of wheezing, coughing and exercise intolerance were significantly different between stage B1, B2 and C affected dogs (P<0.05), with symptoms significantly increasing with disease progression. The proportion of affected dogs with mucosal cyanosis, dyspnea, weakness, abdominal effusion and pericardial effusion was significantly higher in stage C compared to stage B1 (P<0.05) and the proportion of affected dogs with these symptoms in stage B2 was not significantly different from that in stages B1 and C (P>0.05). The proportion of affected dogs with syncope and pleural effusion did not differ significantly between the three groups (P>0.05).

There were 27 (11.1%) MMVD dogs without heart murmurs, all of which were in stage B1 and 217 (88.9%) MMVD dogs with heart murmurs. Among those with heart murmurs, 130 (59.9%) had "soft" murmurs (86 grade I/VI and 44 grade II/VI), 27 (12.4%) had "moderate" murmurs (grade III/VI), 37 (17.1%) had "loud" murmurs (grade IV/VI), and 23 (10.6%) had "thrilling" murmurs (18 grade V/VI and 5 grade VI/VI). The analysis was performed only on dogs with heart murmurs (Table 2). Dogs with "loud" and "thrilling" murmurs were more likely to be diagnosed with CHF than those with "soft" and "moderate" murmurs, accounting for 96% of dogs with CHF (Fig. 4-A). CHF was diagnosed in only 1 (1/159) of the MMVD dogs with "soft" murmurs, none of the "moderate" murmurs, 10 (10/36) of the "loud" murmurs and 17 (17/23) of the "thrilling" murmurs. There was no significant difference (P>0.05) in the proportion of dogs with CHF in "soft" and "moderate" classes. The dogs with "soft" and "moderate" murmurs were significantly different from "loud" and "thrilling" (p<0.05). There was also a significant difference (P<0.05) between the dogs with "loud" and "thrilling" murmurs (Table 2; Fig. 4-B). On the other hand, the majority (98.5%) of dogs with "soft" murmurs did not have cardiac remodeling (Fig. 4-B). The majority (90%) of dogs without cardiac remodeling had "soft" murmurs on auscultation (Fig. 4-A). Cardiac remodeling was present in more than 50% of the dogs with a "moderate" murmur, in more than 80% of dogs with a "loud" murmur

Table 2. Distribution of heart murmurs in 217 dogs with MMVD

Variables	Soft	Moderate	Loud	Thrilling
B1	128(98.5%)[bcd]	10(37.0%)[ad]	5(13.5%)[a]	0(0.0%)[ab]
B2	1(0.8%)[bcd]	17(63.0%)[a]	22(59.5%)[a]	6(26.1%)[a]
C	1(0.8%)[cd]	0(0.0%)[cd]	10(27.0%)[abd]	17(73.9%)[abc]
Totally	130	27	37	23

[a]Statistically different compared to Soft group. [b]Statistically different compared to Moderate group. [c]Statistically different compared to Loud group. [d]Statistically different compared to Thrilling group.

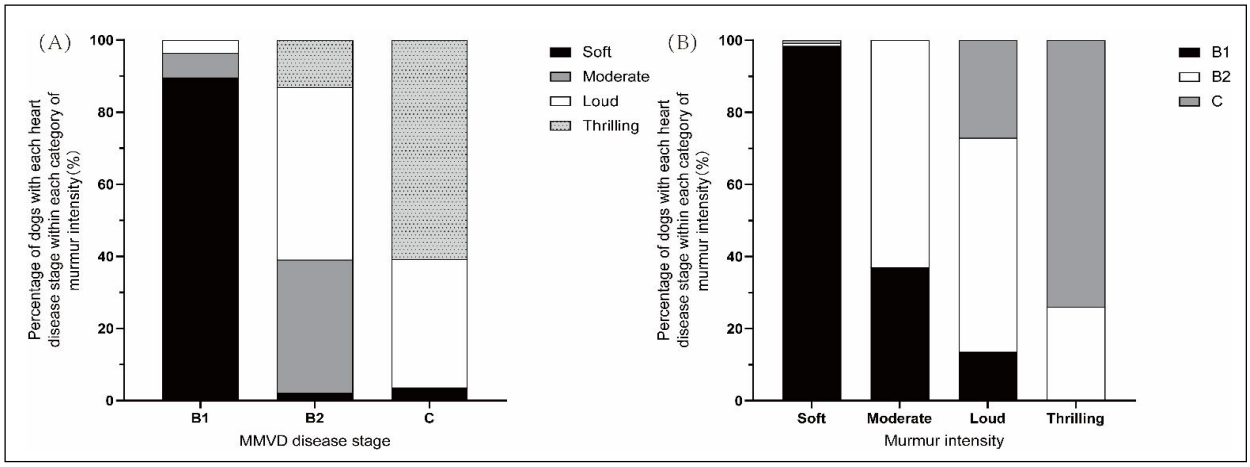

Fig. 4. An increase in murmur intensity is indicative of a higher probability of heart failure. (A) The distribution of murmur intensity across different categories of disease severity reveals a correlation. (B) The prevalence of disease severity within various categories of murmur intensity is also noteworthy. Specifically, B1 represents no signs of cardiac remodeling, B2 signifies subclinical disease accompanied by evidence of cardiac remodeling, and C denotes congestive heart failure

and in all dogs with "thrilling" murmurs (Fig. 4-B). In non-CHF, dogs with "soft" murmurs were significantly different (P<0.05) from "moderate", "loud", and "thrilling" murmurs and there was no significant difference (P>0.05) between the dogs with "moderate", "loud", and "thrilling" (Table 2; Fig. 4-B).

Echocardiographic characteristics: All dogs with MMVD exhibited MR. The maximum MR velocity ranged from 1.08 to 7.04 m/sec (median 5.06, IQR: 4.32-5.52 m/sec). TR developed in 92 dogs with MMVD, with a maximum TR velocity ranging from 1.36 to 4.73 m/sec (median 2.48, IQR: 2.09-2.85 m/sec). AR was observed in 16 dogs with MMVD, with a maximum AR velocity ranging from 1.18 to 4.55 m/sec (median 3.02, IQR: 2.53-4.13 m/sec). PR was present in 25 dogs with MMVD, with a maximum PR velocity ranging from 0.67 to 2.65 m/sec (median 1.74, IQR: 1.41-1.99 m/sec). Maximum flow velocities in the aorta and pulmonary artery were measured in all dogs, with maximum velocities ranging from 0.45 to 1.80 m/sec (median 0.90, IQR: 0.78-1.04 m/sec) and 0.36 to 3.30 m/sec (median 0.73, IQR: 0.60-0.85 m/sec), respectively.

The median LA/AO was 1.40 (IQR: 1.26-1.70), the median LVIDdn was 1.51 (IQR: 1.39-1.77), the median FS was 46.00% (IQR: 40.81-50.00), and the median E-Vel was 0.70 m/sec (IQR: 0.58-0.96 m/sec).

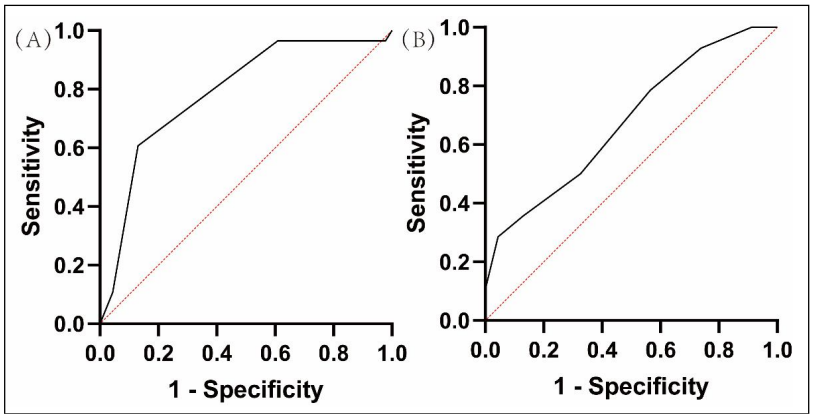

Fig. 5. Cardiac remodeling is characterized by an increase in murmur intensity and a Mine score, which serve as effective predictors of congestive heart failure. (A) The ROC curve for murmur intensity in dogs from groups B2 and C demonstrates its predictive capability. (B) Similarly, the ROC curve for the Mine score in dogs from groups B2 and C highlights its effectiveness as a predictor

Table 3. Echocardiographic characteristics of 244 dogs with MMVD

Variables	B1	B2	C	P value	P value
LA/AO	1.32 (1.20-1.41)	1.80 (1.68-2.00)	1.99 (1.83-2.37)	p<0.01	B1- B2: p<0.01 B1- C: p<0.01 B2- C: p= 0.946
LVIDDn	1.44 (1.34-1.55)	1.89 (1.73-2.00)	1.98 (1.79-2.25)	p<0.01	B1- B2: p<0.01 B1- C: p<0.01 B2- C: p=1.000
FS(%)	44.72 (39.86-49.36)	48.30 (44.54-52.85)	49.00 (45.23-55.84)	p<0.01	B1- B2: p<0.01 B1- C: p<0.01 B2 - C: p=1.000
E-Vel(m/s)	0.61 (0.53-0.0.72)	1.16 (1.09-1.32)	1.15 (0.93-1.37)	P<0.01	B1- B2: p<0.01 B1- C: p<0.01 B2 - C: p=1.000

[a]LA/AO: left atrium-to-aorta ratio; LVIDDn: left ventricular end-diastolic diameter normalized for body weight; FS: left ventricular fractional shortening; E-Vel: E-wave transmitral peak velocity.

The results of non-parametric tests indicated that LA/AO, LVIDdn, FS and E-Vel were statistically different in stage B1 from stage B2 and stage C (P<0.01) but there was no statistically significant (P>0.05) difference between stage B2 and stage C (Table 3). A total of 244 dogs (n=244) with MMVD were scored using the Mine score, with 142 in the "mild" grade, 54 in the "moderate" grade, 47 in the "severe" grade, and only 1 in the "last stage" grade, which belonged to CHF. All dogs with MMVD in the "mild" grade were free of CHF, which was diagnosed in 6 cases (6/54) in the "moderate" grade and in 20 cases (20/47) in the "severe" grade. There was a significant difference (P<0.05) in the proportion of dogs with CHF between

Table 4. Distribution of Mine scores in 244 dogs with MMVD

Variables	Mild	Moderate	Severe	Last stage
B1	138(97.2%)[bcd]	32(59.3%)[ac]	0(0.0%)[ab]	0(0.0%)[a]
B2	4(2.8%)[bc]	16(29.6%)[a]	26(55.3%)[a]	0(0.0%)
C	0(0.0%)[bcd]	6(10.0%)[acd]	20(43.5%)[ab]	1(100%)[ab]
Totally	142	54	47	1

[a]Statistically different compared to the Mild group. [b]Statistically different compared to the Moderate group. [c]Statistically different compared to the Severe group. [d]Statistically different compared to the Last stage group.

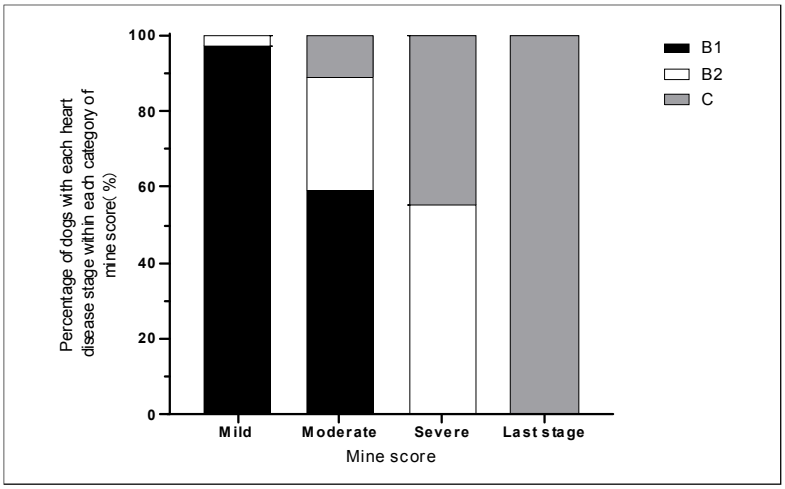

Fig. 6. The intensity of murmurs, classified into three categories. B1 indicates no signs of cardiac remodeling; B2, where subclinical disease is present alongside evidence of cardiac remodeling; and C, which signifies congestive heart failure. Mine score: Mitral Insufficiency Echocardiographic score

the "mild", "moderate", and "severe" grades with no significant difference (P>0.05) between "moderate" and "severe"(Table 4). None of the cases in the "severe" and "last stage" grades were in stage B1 and the proportion of dogs with CHF increased with the higher grade of the Mine score (Fig. 6). The ROC curve result for Mine score was significant for diagnosing the presence of CHF in dogs with MMVD with cardiac remodeling (stages B2 and C), and was a good indicator for diagnosing the presence of CHF (AUC of 0.678, P = 0.11<0.05 (Fig. 5-B). Mine scores≥10.5 had a sensitivity of 28.6% and specificity of 95.7% for predicting the development of CHF in dogs with MMVD with cardiac remodeling.

DISCUSSION

The study found that Stage B1 dogs, which exhibit no cardiac-related clinical signs and are typically detected through physical examination, comprised the largest group. This underscores the increasing importance of thorough physical examinations in contemporary veterinary practice. Stage B2 dogs, which may present with wheezing and coughing after exercise, are often overlooked by their owners, leading to a smaller number of cases compared to Stage B1. Stage C dogs, which often suffer from systemic diseases such as kidney or endocrine disorders, may succumb to non-cardiac factors before a definitive MMVD diagnosis can be made, resulting in a smaller count.

The majority of the dogs in this study were small breeds, in line with previous research (Borgarelli *et al.*, 2004) indicating that MMVD is more prevalent in small-breed dogs. Studies have linked the higher incidence of MMVD in small breeds to genetic factors regulating growth, such as the insulin-like growth factor pathway (Burchell and Shoeman, 2014). The breeds most commonly affected in this study included Poodles, Pomeranians, and Bichons, with King Charles Spaniels, Dachshunds, and Chihuahuas also showing a higher susceptibility to MMVD, consistent with findings in other regions. The distribution of MMVD-prone breeds varies across regions, suggesting that breed surveys will yield different results depending on the area studied. The median weight of the dogs in this investigation was 5.1kg, indicating no significant difference in body weight among dogs in Stages B1, B2, and C, suggesting that MMVD prevalence is more closely associated with breed size rather than body weight, in line with previous studies (Burchell and Shoeman, 2014; O'Brien *et al.*, 2021).

The median age of MMVD-affected dogs in this study was 10 years, similar to previous reports in certain breeds such as Poodles, Dachshunds, Schnauzers and Yorkshire Terriers which range from 7 to 13 years of age (Bussadori *et al.*, 2000; Garncarz *et al.*, 2013; Meurs *et al.*, 2019; DeProspero *et al.*, 2021). The study identified several dogs with early-onset MMVD under the age of 3 years, with Pomeranians leading the count, followed by Bichons and Poodles. The youngest MMVD-affected dog was only 6 months old, suggesting that early onset may be influenced by genetic factors (Borgarelli and Shoeman, 2004; Serfass *et al.*, 2006) and endocarditis (Previti *et al.*, 2024;

Romito *et al.*, 2024). However, the study did not explore the parental generation or the type of myocardial injury in MMVD-affected dogs (Mattin *et al.*, 2015) found a strong correlation between the occurrence of MMVD and the age of the dogs, attributed to the progressive degeneration of the mitral valve with age. The current study conducted the ROC curve analysis to determine the sensitivity of metrics related to heart remodeling (in the absence of CHF) and the development of CHF (in the presence of cardiac remodeling) to age. The ROC curve for age was found to be difficult to distinguish between Stages B2 and C. An age greater than or equal to 9.5 years was identified as a potential cut-off for Stages B1 and B2, potentially serving as a prognostic reference for veterinary practitioners in the clinical diagnosis of cardiac remodeling.

Twenty-seven dogs with MMVD exhibited no heart murmur upon auscultation, highlighting the limitations of auscultation alone in detecting mitral regurgitation, consistent with previous studies (Borgarelli *et al.*, 2012; Adler and Tidholm 2023). The low sensitivity of auscultation may be due to factors such as the noisy environment, the anatomical thoracic structure of the affected dog, the veterinarian's experience level and the human ear's inability to detect low-amplitude sounds. Previous reports have demonstrated that the intensity of the murmur is directly proportional to the severity of mitral regurgitation (Ljungvall *et al.*, 2009). Mild murmurs in small dogs have been reported, with retrospective analyses suggesting they are indicative of heart disease and higher-order heart murmurs associated with more severe MMVD (Ljungvall *et al.*, 2014). The current study employed a four-level classification of heart murmurs (Ljungvall *et al.*, 2014).

The current investigation has revealed that dogs with MMVD stages B1 and B2 also exhibit clinical signs associated with heart disease, which is consistent with findings from previous studies (Ferasin and Linney, 2019). A portion of small dogs in stage B1 present with airway disease, manifesting non-cardiogenic respiratory signs such as coughing and exercise intolerance due to bronchial compression by the dilated left atrium. Dogs in stage B2, characterized by further cardiac remodeling and dilatation, typically experience symptoms like coughing and exercise intolerance as result of left atrial compression of the bronchi. Interestingly, the sole dog in this study with corpora cavernosa in stage B2 had a testicular tumor unrelated to cardiac disease. Clinical symptoms directly attributable to heart disease become more pronounced in stage C, where most dogs exhibit coughing, shortness of breath, and exercise intolerance due to pulmonary edema resulting from left-CHF. When the heart develops pulmonary hypertension or right-CHF, cardiogenic corpora cavernosa may develop (Reinero *et al.*, 2020).

The dogs in this investigation with MMVD exhibited MR velocities greater than 6 m/sec, which may be associated with hypertension and endocarditis diseases (Ventura *et al.*, 2005). A proportion of MMVD dogs have a TR velocity greater than 3 m/sec, which may be indicative of secondary type II pulmonary hypertension (Reinero *et al.*, 2020). TR velocities less than 3 m/sec are generally considered physiological (Adin and McCloy, 2004) or related to anthropogenic measurements (Zoghbi *et al.*, 2003). LA/AO and LVIDdn represent evidence of cardiac remodeling. As MMVD progresses, the LV and LA dilate. LA/AO and LVIDdn will reflect the response to cardiac dilatation (Hansson *et al.*, 2002; Cornell *et al.*, 2004). In the present investigation, cardiac remodeling in stage B1 was found to be significantly different from stages B2 and C, but the difference in the degree of remodeling between stage B2 and C was not significant. FS represents the systolic function of the LV of the heart. Due to the presence of regurgitation, the heart undergoes compensatory mechanisms. During the compensatory phase, there is a compensatory increase in cardiac systolic function (Bonagura and Schober, 2009). In the present investigation, it was found that FS in stage B1 was significantly different from stage B2 and C, indicating that cardiac systolic force increases with the development of MMVD, reflecting the function of cardiac compensation. However, the present investigation found no significant difference in FS between stage B2 and stage C, suggesting that FS is not sensitive for predicting the development of CHF in dogs with MMVD. Mitral E-Vel represents LA filling pressure and LV compliance, but in dogs with MMVD, LA filling pressure is more often indicated (Schober *et al.*, 2010). In the present investigation, E-Vel at stage B1 was significantly different from stages B2 and C, suggesting that elevated LA pressure tends to occur after left atrial remodeling. There was no significant difference in E-Vel between stages B2 and C. This likely because some MMVD dogs in stage C have secondary pulmonary hypertension or right-CHF, and the right heart compensates by taking up some of the excess volume of the LA and relieving some of the pressure (Reinero *et al.*, 2020). Nine of the 28 dogs

with stage C in this investigation were secondary to type II pulmonary hypertension, and all of them had an E-Vel of less than 1.5 m/sec. The Mine score incorporates to all the four of these data, and provides an indication of the severity of MMVD in the form of data (Vezzosi *et al.*, 2021). Previous studies have suggested that the MRSI score predicts the time from stage B2 to stage C, and the Mine score has similar predictive value to the MRSI (Vereb *et al.*, 2024). The current study attempted to find the relationship between Mine score and dogs with CHF. The results show that the proportion of dogs with MMVD that have CHF increases significantly as the grade of the Mine score increases. This study analyzed a ROC curve analysis of Mine scores to predict CHF. Prediction of CHF by Mine score$\geq$10.5 has low sensitivity and a high rate of under-diagnosis. Five of the dogs in stage C of this study with Mine scores below 7 (inclusive) had varying degrees of pulmonary hypertension and right-CHF. Due to right heart compensation, the problem of LA volume overload is temporarily resolved, with the right heart taking up the excess volume of the LA, resulting in a decrease in the mitral E-Vel and a corresponding decrease in the Mine score in this group of dogs (Reinero *et al.*, 2020; Vezzosi *et al.*, 2021). Moreover, LV systolic function in stage C dogs progressively decreases with the progression of decompensation (Schober and Baade, 2000), which also affects the results of the Mine score. In conclusion, a Mine score of $\geq$10.5 makes it extremely indicative that a dog with MMVD has CHF, but a score below 10.5 does not accurately indicate that the dog does not have CHF. In aclinical situation, veterinarians have to assess MMVD disease in the context of clinical features and physical examination. When the rest of the indicator points to CHF are suspected and the dog is with a low Mine score, it is possible that the MMVD dog is severely decompensated or has secondary pulmonary hypertension and right-CHF. To test this hypothesis, dogs with MMVD stage C secondary to pulmonary hypertension or right-CHF should be compared and analyzed again separately. Despite our identification of clinical and echocardiographic features that predict CHF, the gold standard for determining CHF is the presence of pulmonary edema in the affected dog as detected on thoracic DR (Keene *et al.*, 2019; vanStaveren *et al.*, 2023). The shortcoming of this study is the relatively large difference in sample size among stage B1, B2, and C, which may affect the accuracy of data analysis.

In conclusion, this study provides valuable insights into the clinical and echocardiographic characteristics of MMVD in dogs, emphasizing the importance of physical examination, the prevalence of MMVD in specific breeds and the diagnostic utility of heart murmurs in the early detection and management of MMVD. Future research should aim to explore the genetic and endocarditis factors influencing early onset of MMVD, as well as the potential for targeted therapies to slow the progression of the disease. Myxomatous valve disease is common in middle-aged and older small dogs. Examination of clinical features such as breed, age, heart murmur, and symptoms in combination with echocardiography can help veterinarians better predict CHF in the clinical setting. The results of this study can be used as a reference by the veterinarians in the diagnosis of MMVD in dogs.

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Author's contributions: QR: Designing of the work, writing – original draft, data collection, data analysis, data interpretation, validation; CL: Supervision, revising it critically for important intellectual content, validation, funding acquisition; LJ, SL, CH: Data collection, revising, validation; MN, Q: Language polishing, revising, validation; YL: Final approval of the version to be published, Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data availability statement: The data of this study is available from the corresponding author on reasonable demand.

Ethical statement: This study was a retrospective, multicenteric, observational investigation conducted over the period from 2021 to 2023.

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