ISTANBUL UNIVERSITY CERRAHPASA

Associated Risk Factors, Staging, and Median Survival Time of Dogs with Degenerative Mitral Valve Disease

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Abstract

Reports on degenerative mitral valve disease in dogs in Malaysia are limited. This retrospective cohort study investigated the association between gender, age group, and breed size with respect to the risk of degenerative mitral valve disease. The median survival time of the dogs in stages B2, C, and D and levels of owners' compliance were also estimated. Canine case records at University Veterinary Hospital, University Putra Malaysia from July 2013 to July 2021 were reviewed. Owners were contacted to ascertain their compliance with the treatments and the current status (deceased/alive) of their pet dog. The risk factors were analyzed through a logistic regression model and median survival time was determined through the Kaplan–Meier estimator curve. In this study, 306 out of 753 (40.6%) dogs with heart disease had degenerative mitral valve disease. Following an adjustment to the age group, small breed size was the only significant risk factor ($p < .001$). Dogs in B2 had the longest median survival time ($p < .001$), while compliance to treatment was associated with longer median survival time in dogs in Stages C ($p = .015$) and D ($p = .001$). The findings of this study may help in motivating owners to pursue long-term treatment and management of dogs with degenerative mitral valve disease.

Keywords: Compliance, degenerative mitral valve disease, dogs, risk factor, survival time

Introduction

Degenerative mitral valve disease (DMVD) is a condition where the mitral valve leaflet becomes elongated, thickened, or nodulated at the edges due to progressive morphological changes (Fox, 2012). Predisposition for DMVD exists in small and medium breeds such as Dachshunds (Olsen et al., 1999), Cocker Spaniels, and especially Cavalier King Charles Spaniels (CKCS) (Häggström et al., 1992). Age was a notable risk factor for dogs with DMVD, where in certain predisposed breeds, the incidence may achieve 100% in senior dogs (Chetboul et al., 2004; Whitney, 1974). Male dogs had a greater risk (Mattin et al., 2015) than females. Although the disease is uncommonly reported among large-breed dogs, it was reported that these affected dogs tend to have faster disease progression compared to small-breed dogs (Borgarelli et al., 2004). Comprising more than 60% of the canine heart disease cases in veterinary centers, DMVD is the most diagnosed heart disease among the dog population locally (Noordin et al., 2022a; Yap et al., 2021).

Management of DMVD patients requires lifelong treatment to support heart function, improve quality of life, and delay disease progression. Survival of DMVD dogs was shown to be prolonged with a single or multidrug treatment (De Madron et al., 2011). However, like in any other long-term disease, the key to successful treatment and management relies on owners' compliance with the prescribed treatment regime. Drug compliance in veterinary medicine may be defined as the extent to which owners adhere to instructions to administer prescribed drugs to their pets (Grave & Tanem, 1999). Locally, data on the effect of compliance on the survival of dogs diagnosed with heart disease remains lacking.

Although gender, age, and breed size were the known risk factors for DMVD, there is still a need to determine whether similar findings applied to the local setting. Differences in terms of owners' awareness, lifestyle, nutrition of the dogs, and breeds of dogs commonly reared may have affected the canine heart disease scenario locally. Therefore, this study explored the association of gender, age group,

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breed sizes, and DMVD in dogs at a local veterinary teaching hospital. The association between the mean survival time (MST) of DMVD dogs at different stages (Keene et al., 2019) with age, gender, breed size, and compliance status were investigated.

Methods

Study Population

This study retrospectively investigated the records of DMVD dogs presented at the University Veterinary Hospital, University Putra Malaysia (UVH-UPM), between July 2013 and July 2020 (7 years). The patient file number of dogs diagnosed with DMVD was obtained from case logbooks from the two units, namely, the Small Animal Clinic and the Diagnostic Imaging Unit. These case files were manually retrieved and re-examined for data collection.

Data Collection and Categorization

The gender of dogs was noted as either male or female, and the neuter status was disregarded. The breed size of the dogs was categorized as small, medium, and large according to American Kennel Club (AKC) classification (Dog Breeds, 2020). The dogs were divided into two age groups: adult (1–7 years old) and senior (>7 years old).

History, signalment, physical examination, radiographic, and echocardiographic findings for each DMVD dog were reviewed (Table 1). Based on all the information obtained, the dogs were staged using the guidelines established by the American College of Veterinary Internal Medicine (ACVIM) (Keene et al., 2019) (Table 2). The DMVD dog patient files with incomplete information were excluded from the study.

Survival Data

Survival time of the DMVD patients was counted from the date of diagnosis until the day of death or the end of the observation period, which was August 31, 2020. The owners were contacted via phone to ascertain the dog's current health status. A minimum of two phone calls on different days were attempted before the owners were considered unreachable. The owners who could not recall their dog's exact deceased date were guided with prompted questions such as "early/mid/end of the year/month" to guesstimate the deceased date. To ascertain the cause of death, owners were also asked about any concurrent diseases and the clinical signs of heart disease. In this study, the endpoints (deceased) related to heart disease were defined as the patients who succumbed to congestive heart failure, sudden death, or humane euthanasia due to poor quality of life following refractory congestive heart failure. Deceased patients with non-heart-related deaths and dog patients that lost to follow up were censored.

Treatment Compliance

Compliance with treatment was defined as dog and owner adherence to the long-term treatment regime (committed pilling and refills) and routine heart checkups with their attending veterinarian either in UVH-UPM or in a private veterinary clinic. As Stage B1 dogs did not require any treatments, only dogs from Stage B2 onward with known compliance status were included in the analysis, and cases with unknown compliance to treatment were excluded.

Table 1.

Information From the Patient Records Considered for Diagnosis and Staging of the Cases

Records	Findings Considered for Diagnosis and Staging
History and signalment	• Age, gender, breed • Client complaints and clinical signs
Physical examination	• Cardiac auscultation findings (rate, rhythm, quality, description of murmurs) • Respiratory system auscultation findings (rate, rhythm, quality, lung sounds)
Radiography	• Radiographs of right lateral and dorsoventral projection of thorax • Vertebral heart score (VHS) (Buchanan et al., 1995) 1. Measurement from the carina to the apex of the heart and measurement of the widest width of the heart, perpendicular to the first line. The two lines are repositioned on the cranial border of the fourth thoracic vertebrae, and the number of vertebras of both measurements was summed. • Vertebral left atrium score (VLAS) (Stepien et al., 2020) 2. A line is drawn from the ventral aspect of the carina to the dorsal part of the intersection of the cardiac silhouette and caudal vena cava. The line is then repositioned and calculated from the cranial border of the fourth thoracic vertebrae. • Evidence of cardiogenic pulmonary edema 3. Increased parenchymal opacity at perihilar region, with unstructured interstitial, alveolar, or mix of both patterns. • Evaluation of pulmonary vessels for evidence of enlargement, following volume overloading
Echocardiography	• Doppler evaluation of mitral valve 1. Color flow Doppler for quantitative assessment of regurgitation. 2. Spectral Doppler for qualitative measurement of jet velocities. • Thickness measurements (mm) at both systole and diastole of: 1. Interventricular septum 2. Left ventricle internal diameter 3. Left ventricle posterior wall Functional indices 1. Fractional shortening (%) 2. Ejection fraction (%) Ratio 1. Left atrium: Aorta (LA:Ao)
Others	• Relevant test findings to help diagnosis (e.g., complete blood count, serum biochemistry tests, cardiac biomarkers)

Table 2.
The ACVIM Staging is Based on Consensus Guidelines for the Diagnosis and Treatment of Myxomatous Mitral Valve Disease in Dogs

Stages	Classification	
A	Dogs with a high risk of developing heart disease but without any apparent structural abnormality at the time of presentation	
B	Dogs with structural heart disease but have never developed clinical signs of heart failure:	
	B1	Asymptomatic dogs without radiographic or echocardiographic evidence of heart remodeling in response to their DMVD
	B2	• Murmur intensity ≥ 3/6 • Echocardiographic LA: Ao ratio in the right-sided short axis view in early diastole ≥1.6 • Left ventricular internal diameter in diastole, normalized for body weight (LVIDDN) ≥1.7 • Breed-adjusted radiographic vertebral heart score (VHS) >10.5
C	Dogs with either current or past clinical signs of heart failure caused by DMVD	
D	Dogs with end-stage DMVD that are refractory to the standard congestive heart failure treatment	

Source: Keene et al. (2019).
Note: ACVIM = American College of Veterinary Internal Medicine; DMVD = degenerative mitral valve disease.

Statistical Analysis
The data collected were tabulated and filtered for redundancy in Microsoft Excel. Data were descriptively analyzed using Statistical Package for Social Sciences version 26 (SPSS Version 26.0, USA). Age was the only continuous variable and hence reported as mean ± standard deviation (SD) with interquartile range (IQR). Categorical variables were presented in numbers. Its proportions are expressed in percentage and 95% confidence interval (CI). Risk factor analysis and Pearson chi-square test were performed to determine the association between risks and heart disease. The odds ratio (OR) of DMVD within the cohort of heart disease cases was determined using logistic regression. The DMVD dogs were dummy variables coded as 1. Based on the univariable model, all factors with significant *p* value of <.05 attained were selected for multiple logistic regression models using a backward likelihood ratio (LR) elimination method to obtain the final model. The final model was chosen based on the largest Nagelkerker r2, and the statistical model assumptions were met. The goodness of the statistical model assumption was met if (i) Hosmer–Lemeshow test was not significant ($p > .05$); (ii) the overall percentage from classification table was >70%; and (iii) the area under the receiver operating characteristic curve (AUC) was >.70.

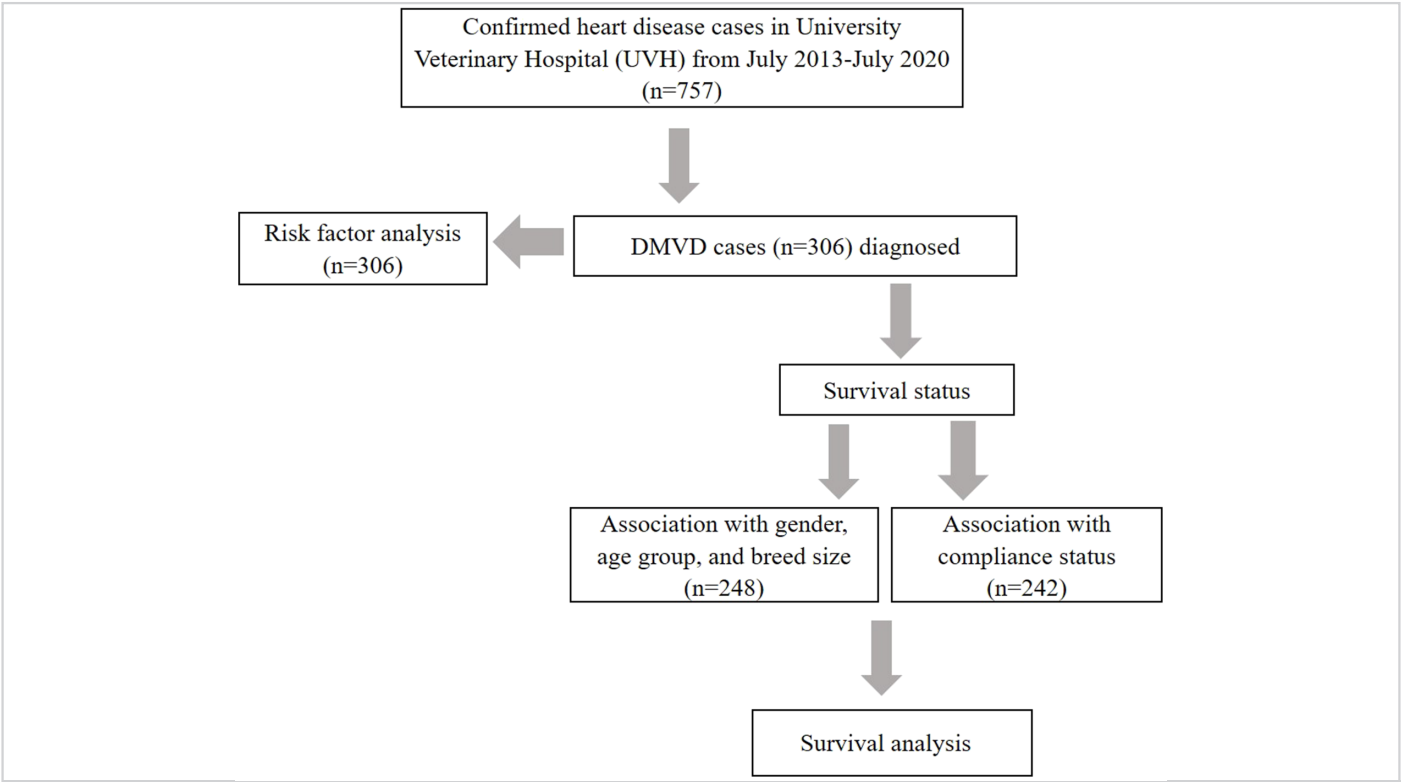

Figure 1.
Outline of Recruited DMVD Dogs Included for Analyses. DMVD, degenerative mitral valve disease.

Table 3.
*Descriptive Analysis of DMVD Dogs (*n *= 306) in UVH-UPM From July 2013 to July 2020*

Profile	Number (n)	Percentage (%)	95% CI (%)
Gender			
Male	156	51.0	45–57
Female	150	49.0	43–55
Age group			
Adult (1–6.9)	50	16.3	13–21
Senior (>7)	256	83.7	79–87
Breed Size			
Small	256	84.3	80–88
Shih Tzu	105	34.3	29–40
Poodle	39	12.7	9–17
Miniature Schnauzer	25	8.2	6–12
Pomeranian	20	6.5	4–10
Miniature Pinscher	18	5.9	4–9
Maltese	11	3.6	2–6
Pug	6	2.0	1–4
Silky Terrier	6	2.0	1–4
Terrier	5	1.6	1–4
Chihuahua	4	1.3	1–3
Pekingese	6	2.0	1–3
Jack Russell Terrier	2	0.7	0–2
Spitz	4	1.3	0–3
Daschund	2	0.7	0–2
Crossbreds	2	0.7	0–2
Papillon	1	0.3	0–2
Medium	45	14.7	11–18
Local	15	4.9	2–7
Cocker Spaniel	13	4.2	1–5
Beagle	5	1.6	1–4
Spitz	4	1.3	
Crossbreds	3	1.0	0–3
Tibetan Spaniel	2	0.3	0–2
Cavalier King Charles Spaniel	3	1.0	1–4
Large	5	1.63	1–4
Golden Retriever	3	0.7	0–2
Dalmatian	2	0.7	0–2
Stages			
B1	9	2.9	2–5
B2	83	27.1	22–32
C	173	56.5	51–62
D	41	13.4	10–18

Note: DMVD = degenerative mitral valve disease; UVH-UPM = University Veterinary Hospital, University Putra Malaysia.

Kaplan-Meier estimate showed the survival curve, and the statistical significance of the survival time was determined using the log-rank test. For logistic regression and Kaplan-Meier Estimate, a p value of $\leq$.05 was accepted as statistical significance.

Results

An outline of cases included for each analysis was summarized in Figure 1. A total of 753 dogs were diagnosed with heart disease, of which 306 (40.6%, 95% CI: 37–44%) dogs had DMVD. The mean age at diagnosis of DMVD dogs was 9.7 years, with an IQR of 8–12 years. The majority of the DMVD dogs were of male, senior aged, small breed, and presented at Stage C of the disease (Table 3).

Out of the 306 DMVD dogs diagnosed, only 242 (79.1%, 95% CI: 74–83%) of the dogs received treatment. At the end of the study observation, only 158 (51.6%) of these cases are with known compliance to the long-term treatment (Table 4).

Risk Factor Analysis

The univariable logistic regression reveals that there was a significant association between age groups and breed size with increased risk of DMVD (Table 5). The multivariate logistic regression model was statistically significant $\chi^2_{(4)} = 135.0$, $p < .001$. The model explained 22.1% of the variance in heart disease and correctly classified 65.1% of dogs. Hosmer and Lemeshow's test for the model was $p = .38$, with a fair AUC of 0.71. When adjusted for breed size, breed size was the only significant risk factor for DMVD. Small-breed dogs were 3.92 times more likely to develop the disease (95% CI 3.08–4.41; $p < .001$) compared to medium-breed dogs.

Survival Analysis

Only 248 (81.0%) out of 306 DMVD dogs were eligible for survival analysis (Figure 1). At the end of the observation period, a total of 148 (59.6%, 95% CI 0.53–0.66) dogs were deceased, with 126 (50.8%, 95% CI 0.79–0.90) death events related to heart disease (Table 6). The mean age for deceased dogs was 11.8 years (IQR; 10.1–13.6 years), while the mean age of dogs that succumbed to heart-related deaths was 12.0 years (IQR; 10.4–14.2 years). Table 7 and Figure 2 show that the DMVD dogs at Stage B2 ($n = 65$) had the longest MST (60.0 months, 95% CI 39.03–82.57, $p < .001$) compared to Stages C and D (Figure 3). Out of the four variables analyzed, age group and treatment compliance had a significant effect on MST ($p < .05$)

Table 4.
*Descriptive Analysis of DMVD Dogs Based on Compliance (*n *= 242) to the Long-Term Treatment*

	Compliance Status					
	Compliant (= 158)			Non-compliant (n = 84)		
Stage	***n***	**%**	**95% CI (%)**	***n***	**%**	**95% CI (%)**
B2	28	11.6	8–16	37	15.3	11–20
C	104	43.0	36–48	37	15.3	11–20
D	26	10.7	7–15	10	4.1	2–7

Note: CI = confidence interval; DMVD = degenerative mitral valve disease; n = number.

Table 5.

*Univariate and Multivariable Logistic Regression Analyses of DMVD Cases Presented to the UVH-UPM between July 2013 and July 2020 (*n = *306) with Risk Factors (Gender, Age Group, and Breed Size)*

						Univariate Logistic Regression			Multivariate Logistic Regression		
Factors	**Total Heart Diseased Dogs (n)**	**DMVD Dogs (n)**	**Percentage**	χ^2	***p***	**b**	**Crude OR (95% CI)**	***p***	***b***	**Adjusted OR (95% CI)**	***p***
Gender				2.03	.150						
Female	346	156	45.1								
Male	407	150	36.9			−.21	0.80 (0.60–1.08)	.150	–	–	–
Age group				115.85	<.001*						
Adult	166	50	30.1				Ref				
Senior	587	256	43.6			.59	1.79 (1.24–2.60)	.002*	.40	1.48 (1.00–2.21)	.060
Breed size				10.45	.005*						
Medium	186	45	23.1				Ref				
Small	468	256	55.1			1.40	4.07 (2.76–6.00)	<0.001*	1.37	3.95 (2.68–5.82)	<0.001*
Large	99	5	5.1			−1.73	0.18 (0.07–0.46)	<0.001*	−1.71	0.18 (0.07–0.47)	<0.001*

Note: *b* = standardized beta; CI = confidence interval; χ^2 = Chi square, DMVD = degenerative mitral valve disease; n = number; OR = odds ratio, Ref = reference; UVH-UPM = University Veterinary Hospital, University Putra Malaysia.
*$p < .05$.

Table 6.

*Descriptive Analysis of DMVD Cases Based on Mortality Status and Cause of Death (*n = *248) Based on the Owner's Observation*

	Stages											
	B1			**B2**			**C**			**D**		
Status	**n**	**%**	**95 CI%**	**n**	**%**	**95 CI%**	**n**	**%**	**95 CI%**	**n**	**%**	**95 CI%**
Alive (n= 82)	6	2.4	0.01–0.05	31	12.5	9–17	39	15.7	12–21	6	2.4	1–5
Deceased (n=148)												
Heart-related death	–	–	–	18	7.3	5–11	81	32.7	27–39	27	10.9	8–15
Non-heart-related deaths	–	–	–	10	4.0	2–7	10	4.0	2–7	2	0.8	0–3
Lost to follow-up (n=18)	–	–	–	6	2.4	1–5	11	4.4	2–8	1	0.4	0–2

Note: n = number; CI = confidence interval; DMVD = degenerative mitral valve disease.

(Table 8). Dogs with owners who were compliant with the treatment prescribed had an additional 23.2 months and 11.9 months after diagnosis compared to the non-compliant group in both stages C and D, respectively (Figures 4 and 5).

Discussion

This study investigated the risk factors of canine DMVD in the local setting. To our knowledge, the current study provides the first survival data of canine DMVD patients presented at the veterinary healthcare facility locally. In addition, the data from this study were obtained from dogs of various breeds and, therefore, may provide a better perspective on canine DMVD.

Senior-aged dogs made up most of the DMVD dogs in this study, and the mean age of 9.7 years old at diagnosis was similar to previous studies (Borgarelli et al., 2008; Mattin et al., 2015). Interestingly, age was not a significant risk factor for DMVD when adjusted for breed size. It can be speculated that age is a significant risk factor, but small breed size has a more significant association with DMVD. However, in this study, DMVD dogs aged more than 7 years old have shorter MST than adult dogs, similar to previous findings (Borgarelli et al., 2008; Häggström et al., 1995).

The breed size was the only significant risk factor for DMVD after adjusting for gender and age group. Findings were consistent with other studies where small breed dogs were frequently diagnosed (Mattin et al., 2015; Yap et al., 2021). With the polygenic trait inheritance pattern established among most predisposed breeds, it was speculated that genetic composition may be responsible for increasing the risk of DMVD in other small-breed dogs. It is hypothesized that

Table 7.
Median Survival Time (MST) of Dogs Diagnosed with DMVD (n = 248) Based on Gender, Age Group, Breed Size and Stages of the Disease

			95% CI		Log Rank Test	
Variables	**Estimate (Months)**	**SE**	**Lower Bound**	**Upper Bound**	χ^2	***p***
Gender						
Male	37.1	6.2	25.0	49.2	0.5	.470
Female	45.4	7.8	30.2	60.6		
Age group (years old)						
Adult (1–6.9)	NA	NA	NA	NA	9.2	.002*
Senior (>7)	34.8	5.4	24.2	45.4		
Breed size						
Small	42.5	3.7	35.3	49.7	3.0	.230
Medium	24.0	7.7	8.9	39.1		
Large	15.1	3.4	8.4	21.8		
Stages						
B1	NA	NA	NA	NA	31.9	<.001*
B2	60.8	3.3	54.4	67.2		
C	36.1	6.4	23.5	48.7		
D	14.8	4.5	6.0	23.6		

Note: CI = confidence interval; χ^2 = Chi square; DMVD = degenerative mitral valve disease; NA = not available; SE = standard error.
*$p < .05$.

alteration in genes, such as insulin-like growth factor 1 is responsible for the reduction in body size and disproportionate decrease in the size of the heart and its related structures, predisposing the valve to the disease due to entrapment in the chest cavity (Raggi et al., 2000; Wang et al., 1999). Alteration in polygenic traits that are responsible for the maintenance and repair of valvular structures, such as collagen, proteoglycan, and hyaluronan (Madsen et al., 2011), may lower the valve tolerance to the workload over time. In terms of breed,

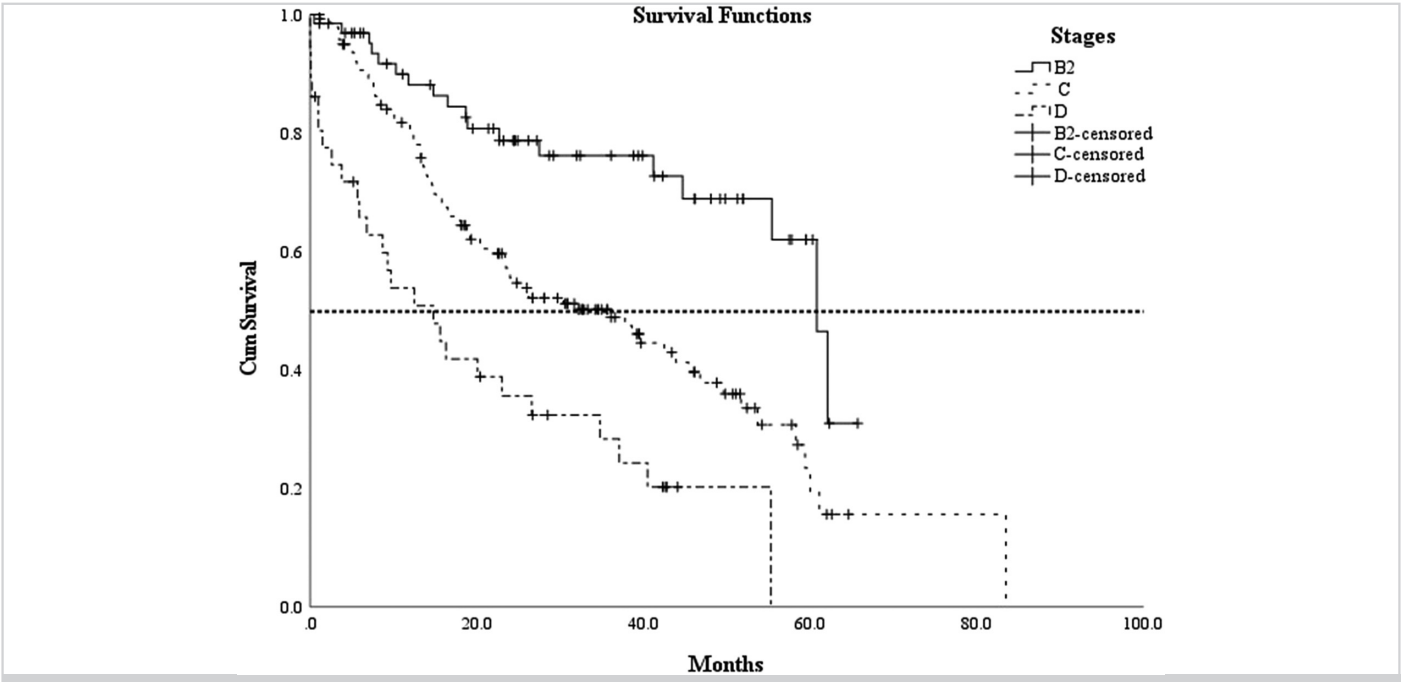

Figure 2.
Kaplan-Meier Estimator Curve of DMVD Dogs with Known Survival Status (n = 242) in UVH from July 2013–July 2020. Solid line: Stage B2, dashed line: Stage C, and dash-dotted line: Stage D. DMVD, degenerative mitral valve disease; UVH, University Veterinary Hospital.

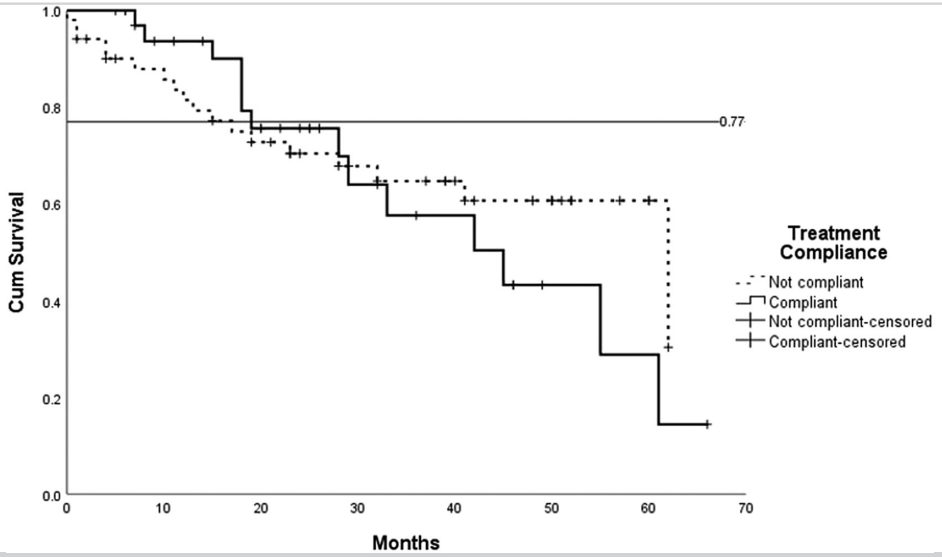

Figure 3.
Kaplan-Meier Estimator Curve of Stage B2 DMVD (n = 65) dogs with Owner Compliance to Treatment Versus Non-compliance. Solid line: compliant cases, dashed lines: non-compliant cases, dotted line: median. DMVD, degenerative mitral valve disease.

Table 8.
Median Survival Time of dogs Diagnosed with DMVD at Different Stages and the Effect of Survival Based on Treatment Compliance (n = 242)

				95% CI		Log Rank Test	
Stages	**Compliance Status**	**Estimate (months)**	**SE**	**Lower Bound**	**Upper Bound**	**χ2**	***p***
B2	Compliant	48.47	4.69	39.28	57.65	0.12	.73
	Non-compliant	49.12	3.77	41.80	56.57		
C	Compliant	42.11	3.25	35.74	48.48	11.60	<.001*
	Non-compliant	25.04	3.99	17.23	32.86		
D	Compliant	25.23	4.06	17.27	33.20	7.20	.007*
	Non-compliant	7.00	3.65	0.000	14.14		

Note: CI = confidence interval; DMVD = degenerative mitral valve disease; χ^2 = Chi square; SE = standard error.
*$p < .05$.

in this study, the Shih Tzu dogs were greatly affected followed by Poodle and Miniature Schnauzer. Shih Tzus were known to have an increased risk for DMVD (Mattin et al., 2015) and were among the common breeds affected by the disease (Borgarelli & Buchanan, 2012; Serfass et al., 2006). Specific studies on these breeds in relation to DMVD are still lacking, and further investigation may help in elucidating the disease process in this breed.

In this study, most of the DMVD dogs presented at the hospital were in Stage C. As expected, the presence of clinical signs such as coughing and exercise intolerance prompted the owners to bring their pet dogs for a veterinary checkup. Although the awareness of canine heart disease is high among dog owners locally, their ability to identify clinical signs related to heart disease was moderate, which may have led to this finding (Noordin et al., 2022b). Furthermore, clinical signs of heart disease in dogs may be mistaken for mild respiratory illness or old age. Hence, it can be speculated that most owners took the "wait and see" approach and only sought veterinarian attention when clinical signs observed did not resolve or got worsened.

In a lifespan study involving more than 30,000 dogs, MST of dogs is 14.3 years (Urfer et al., 2020). Considering the mean age at diagnosis in this study is 9.7 years old and MST of Stage B2 dogs is 60.8 months (5.09 years), in the least severe stage of DMVD, the dog's survival is roughly comparable to the normal dogs' lifespan (15.6 years). In the study population, there were more heart-related deaths among dogs in the study compared to non-heart-related deaths. The highest number of deaths was seen in Stage D, in which the shortest MST was recorded between other stages. Among DMVD patients, morbidity of the disease is proportional to the magnitude of valvular insufficiency and volume overload (Fox, 2012). With severe insufficiency, volume overload occurs faster as a result of the chronic increase in end-diastolic volume and subsequent remodelling of the left atrium. Furthermore, as congestive heart failure becomes refractory, secondary complications such as kidney failure may follow suit, which

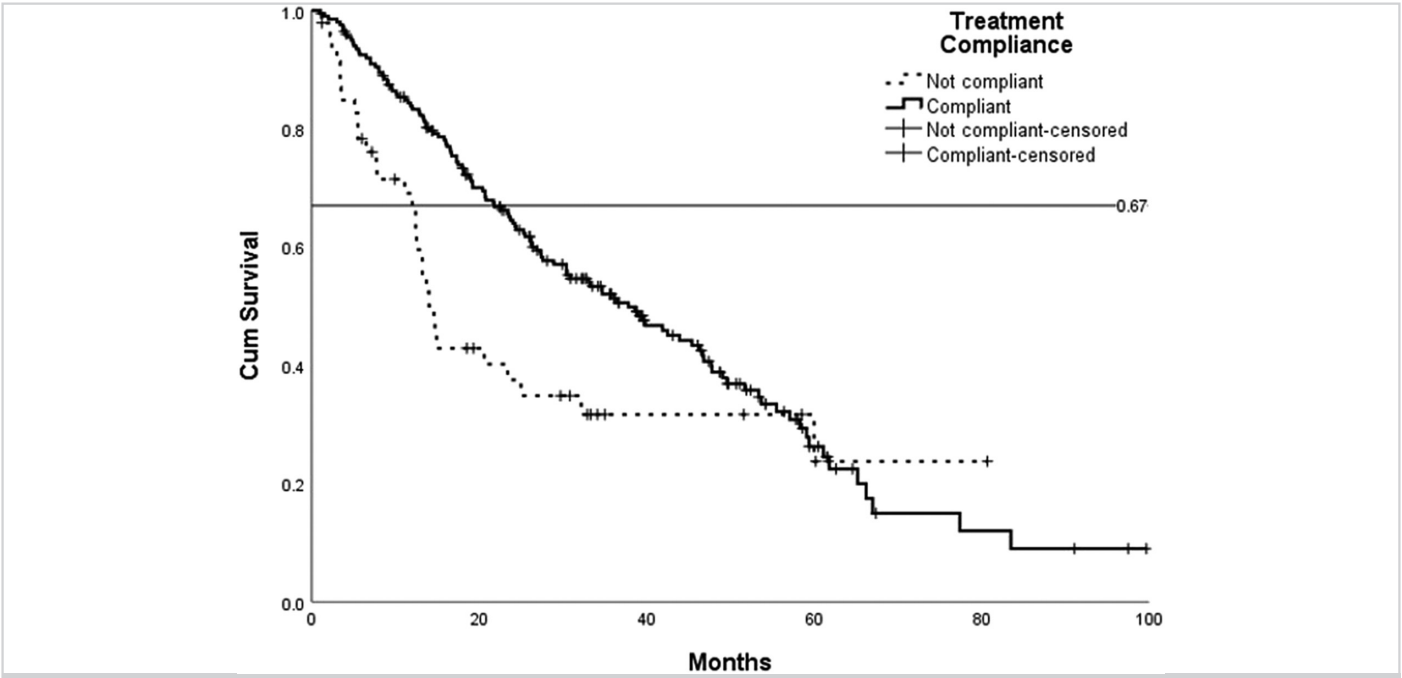

Figure 4.
*Kaplan-Meier Estimator Curve of Stage C DMVD (*n = *141) Dogs with Owner Compliance to Treatment Versus Non-Compliance. Solid line: compliant cases, dashed lines: non-compliant cases, dotted line: median. DMVD, degenerative mitral valve disease.*

may predispose the patients to shorter MST (Pouchelon et al., 2015). Although the cause of death in each dog was not investigated, the researchers carefully reviewed the incident as verbally described by their respective dog owners. Information obtained was reviewed with an experienced clinician before including the dog patients for survival analysis in this study.

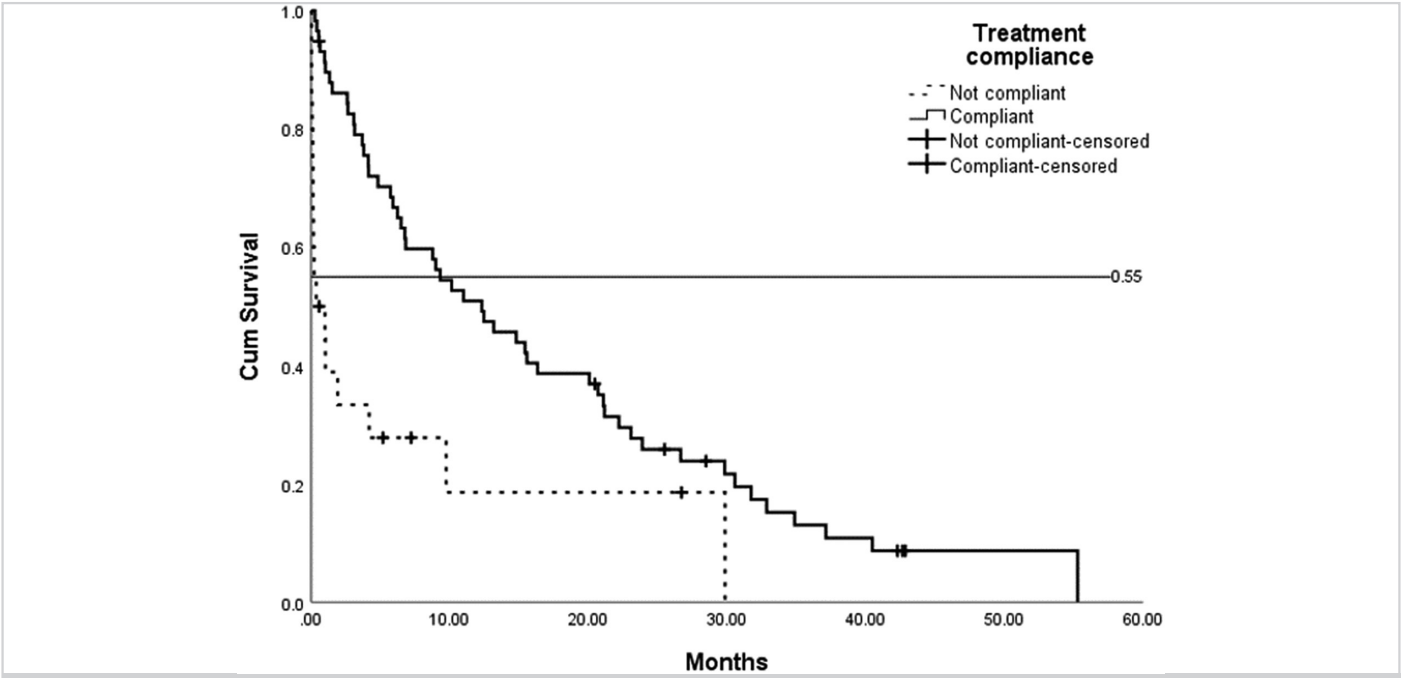

Figure 5.
*Kaplan-Meier Estimator Curve of Stage D DMVD (*n = *36) Dogs with Owner Compliance to Treatment Versus Non-compliance. Solid line: compliant cases, dashed lines: non-compliant cases, dotted line: median. DMVD, degenerative mitral valve disease.*

Breed-specific studies found that male dogs have faster disease progression than females in certain predisposed breeds such as Cavalier King Charles Spaniel and Daschunds (Olsen et al., 1999; Swenson et al., 1996). However, in this study, the difference between MST of female and male dogs was both non-significant, in agreement with previous multi-breed studies (Borgarelli et al., 2008; Häggström et al., 1995; Kim et al., 2017).

In any type of progressive or chronic disease, dog owners' compliance with the long-term medication prescribed is vital to achieving successful disease management and ensuring the quality of life of the affected dogs (Talamonti et al., 2015). Degenerative mitral valve disease is a progressive disease where continuous treatment and a tailor-made regime are imperative to support heart functions, aiming to reduce clinical signs and prolong the lifespan of the affected dogs. Although factors such as cost, time (Noordin et al., 2022b), size of the pill, and taste of medication are among the challenges in the management of dog heart disease patients, compliance among owners of these dogs is high (Pelio et al., 2021). It is known that the quality of life of the dog was a top priority among owners with advanced heart disease dogs (Oyama et al., 2008). In the current study, despite the majority requiring more than one long-term medication, dogs in Stage C had a higher number of compliant owners. It can be speculated that the presence of clinical signs that affected their dogs' quality of life creates an urgency to comply with the prescriptions. Furthermore, improvement of clinical signs and recurrence following non-compliance may motivate the owners to adhere to the drug prescription. In contrast, the compliance level among owners of Stage D patients is much lower. Through the phone interviews, it was found that owners either prefer to lessen the burden on their animals by not proceeding with aggressive treatments or are cost-constrained to pursue further treatments.

American College of Veterinary Internal Medicine outlined pharmacological intervention in canine DMVD patients, and therapeutic intervention began as early as Stage B2 (Keene et al., 2019). Preclinical DMVD dog patients treated with pimobendan (0.4–0.6 mg/kg/day) were found to have significantly higher MST than the placebo group (Boswood et al., 2016). In the current study, however, there were no significant differences in MST between compliant and non-compliant cases in Stage B2, presumably due to a small number of dogs, of which 12% had non-heart-related deaths. We believed that a larger sample of Stage B2 dogs may properly elucidate the efficacy of compliance to the treatment. Furthermore, anecdotal observation during data collection found that most dogs in DMVD Stage B2 did not return for follow-ups as advised. Therefore, by the time the study was conducted, it is unclear as to whether the DMVD Stage B2 dogs' heart condition had progressed and whether no treatment provided had contributed to poor MST.

The highlight of this study is the significantly higher MST among the dogs in Stages C and D with owners that are compliant with treatment. Continuous treatment is imperative to support heart functions, reducing clinical signs and prolonging the lifespan of the affected dogs. Other than continuous medication, compliance also ensures periodical heart checkups with veterinarians. This may allow the dog to be constantly re-evaluated over the years and allow adjustment in the long-term treatment according to the dog's current conditions, thus preserving the treatment efficacy.

Due to the retrospective nature of this study, the finding should be interpreted with a background of limitations. The different types of heart medications prescribed vary between dogs. Therefore, survival analyses based on specific drugs were not carried out. Similarly, the dosage increment may influence the medication performance in extending the MST. However, the exact role of medication was not covered in this study as there were many confounding factors such as cost, skills of drug administration, and owners' time constraints that influence the choice of drugs and management of the DMVD dogs.

Conclusion

In a cohort of heart disease patients, there is an increased risk of DMVD among small-breed dogs compared to other heart diseases. Senior dogs have shorter MST compared to adults. Despite the presence of clinical signs and extensive changes to the heart, correct treatment and a good level of compliance can still assist in extending the lifespan of dogs in clinical stages. Therefore, owners must be encouraged and motivated to pursue and comply with medications prescribed and regular revisits.

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References

Borgarelli, M., Savarino, P., Crosara, S., Santilli, R. A., Chiavegato, D., Poggi, M., Bellino, C., La Rosa, G., Zanatta, R., Haggstrom, J., & Tarducci, A. (2008). Survival characteristics and prognostic variables of dogs with mitral regurgitation attributable to myxomatous valve disease. *Journal of Veterinary Internal Medicine*, *22*(1), 120–128. [CrossRef]

Borgarelli, M., Zini, E., D'Agnolo, G., Tarducci, A., Santilli, R. A., Chiavegato, D., Tursi, M., Prunotto, M., & Häggström, J. (2004). Comparison of primary mitral valve disease in German Shepherd dogs and in small breeds. *Journal of Veterinary Cardiology*, *6*(2), 27–34. [CrossRef]

Borgarelli, M., & Buchanan, J. W. (2012). Historical review, epidemiology and natural history of degenerative mitral valve disease. *Journal of Veterinary Cardiology*, *14*(1), 93–101. [CrossRef]

Boswood, A., Häggström, J., Gordon, S. G., Wess, G., Stepien, R. L., Oyama, M. A., Keene, B. W., Bonagura, J., MacDonald, K. A., Patteson, M., Smith, S.,Fox, P. R., Sanderson, K., Woolley, R., Szatmári, V., Menaut, P., Church, W. M., O'Sullivan, M. L., Jaudon, J. P., Rush J., Barrett K.A., Rosenthal S.L., Saunders A.B., Ljungvall I., Deinert M., Bomassi E., Estrada A.H., Fernandez Del Palacio M.J., Moise N.S., Abbott J.A., Fujii Y., Spier A., Luethy M.W., Santilli R.A., Uechi M., Tidholm A., Watson P. (2016). Effect of pimobendan in dogs with preclinical myxomatous mitral valve disease and cardiomegaly: The EPIC study—A randomized clinical trial. *Journal of Veterinary Internal Medicine*, *30*(6), 1765–1779

Buchanan, J. W., Sci, M., Bucheler, J., & Ver, M. (1995). Vertebral scale system to measure canine heartsize in radiographs. *Journal of the American Veterinary Medical Association*, *206*(2). 194-199

Chetboul, V., Tissier, R., Villaret, F., Nicolle, A., Déan, E., Benalloul, T., & Pouchelon, J. L. (2004). Caractéristiques épidémiologiques, cliniques, échodoppler de l'endocardiose mitrale chez le Cavalier King Charles en France: Étude retrospective de 451 cas (1995 à 2003). *Canadian Veterinary Journal*, *45*(12), 1012–1015.

De Madron, E., King, J. N., Strehlau, G., & Valle White, R. V. (2011). Survival and echocardiographic data in dogs with congestive heart failure caused by mitral valve disease and treated by multiple drugs: A retrospective study of 21 cases. *Canadian Veterinary Journal*, *52*(11), 1219–1225.

Dog breeds. (2020). American Kennel Club. Retrieved January 5, 2020, from https://www.akc.org/dog-breeds/

Fox, P. R. (2012). Pathology of myxomatous mitral valve disease in the dog. *Journal of Veterinary Cardiology*, *14*(1), 103–126. [CrossRef]

Grave, K., & Tanem, H. (1999). Compliance with short-term oral antibacterial drug treatment in dogs. *Journal of Small Animal Practice*, *40*(4), 158–162. [CrossRef]

Häggström, J., Hansson, K., Kvart, C., & Swenson, L. (1992). Chronic valvular disease in the cavalier King Charles Spaniel in Sweden. *Veterinary Record*, *131*(24), 549–553.

Häggström, J., Kvart, C., & Hansson, K. (1995). Heart sounds and murmurs: Changes related to severity of chronic valvular disease in the Cavalier King Charles Spaniel. *Journal of Veterinary Internal Medicine*, *9*(2), 75–85. [CrossRef]

Keene, B. W., Atkins, C. E., Bonagura, J. D., Fox, P. R., Häggström, J., Fuentes, V. L., Oyama, M. A., Rush, J. E., Stepien, R., & Uechi, M. (2019). ACVIM consensus guidelines for the diagnosis and treatment of myxomatous mitral valve disease in dogs. *Journal of Veterinary Internal Medicine*, *33*(3), 1127–1140. [CrossRef]

Kim, H. T., Han, S. M., Song, W. J., Kim, B., Choi, M., Yoon, J., & Youn, H. Y. (2017). Retrospective study of degenerative mitral valve disease in small-breed dogs: Survival and prognostic variables. *Journal of Veterinary Science*, *18*(3), 369–376. [CrossRef]

Madsen, M. B., Olsen, L. H., Häggström, J., Höglund, K., Ljungvall, I., Falk, T., Wess, G., Stephenson, H., Dukes-McEwan, J., Chetboul, V., Gouni, V., Proschowsky, H. F., Cirera, S., Karlskov-Mortensen, P., & Fredholm, M. (2011). Identification of 2 loci associated with development of myxomatous mitral valve disease in Cavalier King Charles Spaniels. *Journal of Heredity*, *102*, Suppl. 1, S62–S67. [CrossRef]

Mattin, M. J., Boswood, A., Church, D. B., López-Alvarez, J., McGreevy, P. D., O'Neill, D. G., Thomson, P. C., & Brodbelt, D. C. (2015). Prevalence of and risk factors for degenerative mitral valve disease in dogs attending primary-care veterinary practices in England. *Journal of Veterinary Internal Medicine*, *29*(3), 847–854. [CrossRef]

Noordin, N., Hua Khor, K., Lee Ee, K., Lau, S. F., & Ramanoon, S. Z. (2022a). Risk factors for heart disease in pet dogs attended at a Veterinary Teaching Hospital in Malaysia. *International Journal of Veterinary Science*, *11*(4), 504–513. [CrossRef]

Noordin, N., Khor, K. H., Khor, K. S., Lim, Y. J., & Lee, Y. C. (2022b). Dog owners' perspectives on canine heart disease in Klang Valley, Malaysia. *Animals: An Open Access Journal from MDPI*, *12*(8), 985. [CrossRef]

Olsen, L. H., Fredholm, M., & Pedersen, H. D. (1999). Epidemiology and inheritance of mitral valve prolapse in Dachshunds. *Journal of Veterinary Internal Medicine*, *13*(5), 448–456. [CrossRef]

Oyama, M. A., Rush, J. E., O'Sullivan, M. L., Williams, R. M., Rozanski, E. A., Petrie, J. P., Sleeper, M. M., & Brown, D. C. (2008). Perceptions and priorities of owners of dogs with heart disease regarding quality versus quantity of life for their pets. *Journal of the American Veterinary Medical Association*, *233*(1), 104–108. [CrossRef]

Pelio, D. C., Russell, N. J., Passley, B. S., Rosson, C. D., Weller, J. B., Malouf, K. A., Murphy, L. A., & Nakamura, R. K. (2021). Evaluation of owner medication adherence for canine cardiovascular disease in the referral setting. *Journal of Veterinary Cardiology*, *37*, 42–51. [CrossRef]

Pouchelon, J. L., Atkins, C. E., Bussadori, C., Oyama, M. A., Vaden, S. L., Bonagura, J. D., Chetboul, V., Cowgill, L. D., Elliot, J., Francey, T., Grauer, G. F., Fuentes, V. L., Moise, N. S., Polzin, D. J., Van Dongen, A. M., & Van Israël, N. (2015). Cardiovascular-renal axis disorders in the domestic dog and cat: A veterinary consensus statement. *Journal of Small Animal Practice*, *56*(9), 537–552. [CrossRef]

Raggi, P., Callister, T. Q., Lippolis, N. J., & Russo, D. J. (2000). Is mitral valve prolapse due to cardiac entrapment in the chest Cavity? A CT view. *Chest*, *117*(3), 636–642. [CrossRef]

Serfass, P., Chetboul, V., Sampedrano, C. C., Nicolle, A., Benalloul, T., Laforge, H., Gau, C., Hébert, C., Pouchelon, J. L., & Tissier, R. (2006). Retrospective study of 942 small-sized dogs: Prevalence of left apical systolic heart murmur and left-sided heart failure, critical effects of breed and sex. *Journal of Veterinary Cardiology*, *8*(1), 11–18. [CrossRef]

Stepien, R. L., Rak, M. B., & Blume, L. M. (2020). Use of radiographic measurements to diagnose stage B2 preclinical myxomatous mitral valve disease in dogs. *Journal of the American Veterinary Medical Association*, *256*(10), 1129–1136. [CrossRef]

Swenson, L., Häggström, J., Kvart, C., & Juneja, R. K. (1996). Relationship between parental cardiac status in Cavalier King Charles spaniels and prevalence and severity of chronic valvular disease in offspring. *Journal of the American Veterinary Medical Association*, *208*(12). 2009-2012

Talamonti, Z., Cassis, C., Brambilla, P. G., Scarpa, P., Stefanello, D., et.al., (2015). Preliminary Study of Pet Owner Adherence in Behaviour, Cardiology, Urology, and Oncology Fields.*Veterinary Medicine International*, 618216.

Urfer, S. R., Kaeberlein, M., Promislow, D. E. L., & Creevy, K. E. (2020). Lifespan of companion dogs seen in three independent primary care veterinary clinics in the United States. *Canine Medicine and Genetics*, *7*(1), 7. [CrossRef]

Wang, J., Zhou, J., Powell-Braxton, L., & Bondy, C. (1999). Effects of Igf1 gene deletion on postnatal growth patterns. *Endocrinology*, *140*(7), 3391–3394. [CrossRef]

Whitney, J. C. (1974). Observations on the effect of age on the severity of heart valve lesions in the dog. *Journal of Small Animal Practice*, *15*(8), 511–522. [CrossRef]

Yap, K. S., Ghanabadi, S., Ibrahim Abdul-Azeez Okene, A. S., & Ayahsamy, S. (2021). Retrospective Echocardiographic Survey of Canine Cardiac Conditions in Kuala Lumpur, Malaysia. *Journal of Animal Health and Production* Retrospective, *9*(2): 198–204