P-ISSN: 2304-3075; E-ISSN: 2305-4360
International Journal of Veterinary Science
www.ijvets.com; editor@ijvets.com
Research Article https://doi.org/10.47278/journal.ijvs/2022.154

Risk Factors for Heart Disease in Pet Dogs Attended At a Veterinary Teaching Hospital in Malaysia

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Article History: 22-518 Received: 29-Jan-22 Revised: 08-Mar-22 Accepted: 19-Mar-22

ABSTRACT

The distribution and risk factors of canine heart disease in Malaysia are still not widely studied. This retrospective study examined the distribution of common canine heart diseases and the role of gender, age group, and breed size as risk factors of the dogs in a teaching hospital in Malaysia. Medical records of all dogs presented between 2013 and 2020 with a heart disease diagnosed were reviewed and analyzed. Univariate and multivariate logistic regression was carried out to identify the risk factors for canine heart diseases in general and based on specific disease. In a duration of 7 years, a total of 9255 dog cases were presented and 7.9% (n=734, 95% CI: 0.07-0.09) of the dogs were diagnosed with heart disease. Majority of heart disease cases were valvular disease (n=528, 95% CI: 0.05-0.06), followed by heartworm disease (n=113. 95% CI: 0.01-0.01), dilated cardiomyopathy (DCM) (n=90, 95% CI: 0.01-0.01). Senior (OR 3.54, 95% CI: 2.32-5.37) and small breed (OR 6.74, 95% CI: 4.51-10.1) dogs had higher risk for valvular disease, while large breed (OR 7.18, 95% CI: 4.00-13.01) dogs were at risk for heartworm disease. Male (OR 1.83, 95% CI:1.11-3.04) and large breed dogs (OR 3.12, 95% CI: 1.80-5.39) had greater risk for DCM, respectively. Gender, age group and breed size play important role in predicting the likelihood of heart diseases in dogs and are best to be applied in the context of specific heart diseases. Information obtained would assist clinicians with their clinical diagnosis of the heart disease.

Key words: Canine, Cardiovascular, Risk factors, Malaysia, Teaching hospital.

INTRODUCTION

Heart disease is among the common chronic diseases reported in dogs, covering approximately 10.0% of total cases in primary veterinary centres in the United States (Keene et al. 2019). The valvular disease accounts for approximately 80.0% of acquired heart diseases in dogs, followed by cardiomyopathies at 20.0% (Olsen et al. 1999). Other forms such as pericardial effusion (Haritha 2020), endocarditis (Sykes et al. 2006) and cardiac tumour (Ware and Hopper 1999) were reported at a lower occurrence. Congenital heart defect affects 1 in every 15 litters on average and is often seen in dogs compared to cats (Tilley et al. 2008). In dogs, pulmonic stenosis, followed by subaortic stenosis and patent ductus arteriosus (Oliveira et al. 2011; Schrope 2015; Brambilla et al. 2020) is the most common congenital heart defect diagnosed.

The most common type of valvular disease is chronic degenerative valvular disease (CDVD) (Keene et al. 2019) where the affected valves undergo a progressive architectural disruption of the leaflet layer. Mitral valve is commonly affected, followed by tricuspid valves, while other valves are less affected (Borgarelli and Buchanan 2012). Higher occurrences, up to 100% with advancing age, was seen in small and medium breeds such as Cavalier King Charles Spaniels and Daschunds (Chetboul et al. 2004; Serfass et al. 2006).

Dilated cardiomyopathy (DCM) is the most common form of cardiomyopathies in dogs characterized by progressive dilation of ventricles, impaired contractility, and consequently systolic dysfunction (Egenvall et al. 2005). Genetic predisposition was seen in large breed dogs particularly Great Dane, Doberman Pinscher, Boxer, and Newfoundland (Stephenson et al. 2012; Wess 2021) but,

Cite This Article as: Noordin N, Khor KH, Ee KL, Lau SF, and Ramanoon SZ 2022. 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. https://doi.org/10.47278/journal.ijvs/2022.154

may also occur secondary to systemic diseases, toxins, infectious agents, and nutritional deficiencies, particularly taurine and L-carnitine (Tilley et al. 2008). Recently, an increase in reports of reversible DCM progression among non-predisposed breeds raised speculation on the association between grain-free diet and DCM, however, the exact pathophysiology is still poorly understood (Freeman et al. 2018). Canine heartworm disease is caused by filarial nematode *Dirofilaria immitis*, a common disease diagnosed in the tropical region (Simón et al. 2012). Adult heartworms cause damage in the pulmonary artery and right ventricles of the heart resulting in clinical signs such as exercise intolerance, cyanosis, coughing, and dyspnoea (Nelson et al. 2018).

Prediction of heart disease may help veterinarians to make a more precise differential diagnosis especially in the absence of gold standard diagnostics. However, published estimates of distribution and prevalence are currently limited to populations of high-risk breeds and/or based on studies conducted several decades ago (Buchanan 1977; Detweiler and Patterson 1965). Comparison to the local dog population may be limited due to the difference in the common breed reared. Due to the paucity of data on dogs with heart disease locally, this study objective was to analyse the distribution and risk factors of canine heart diseases among the dog population presented to a veterinary teaching hospital in Peninsular Malaysia from July 2013 to July 2020.

MATERIALS AND METHODS

Study Design

A retrospective data analysis using medical records of dog patients presented to University Veterinary Hospital (UVH) of Universiti Putra Malaysia (a primary veterinary healthcare facility) from July 2013 to July 2020 (7 years). The total numbers of dogs presented and the total numbers of dogs diagnosed with heart disease were obtained from the Small Animal Clinic canine cases logbooks. Information obtained was confidential and was only used for research purposes. This study has obtained approval from UVH prior to commencement.

Definition of Diseases

Valvular diseases were defined as evidence of echocardiography exhibiting thickening, elongated, or prolapsed valvular leaflets with regurgitation in the Doppler study. Similarly, DCM was characterized by echocardiography with findings of moderate to severe left ventricular and atrial enlargement, reduced systolic function, and reduced fractional shortening to less than 25% (Tilley et al. 2008). Heartworm disease was defined by positive results of relevant test kits or diagnostic methods such as SNAP® 4Dx® (IDEXX Laboratories, US), modified Knott's test, or observation of microfilariae in direct blood smear.

Criteria of other diseases were diagnosed as per described in published textbooks (Tilley et al. 2008). The cases were divided into two categories, namely diagnosed and suspected cases. Diagnosed cases were defined as dogs with a final diagnosis of heart disease recorded in the files, supported by affirmative findings from radiography and echocardiography (Esaote MyLabTM Class C) with/without other information such as electrocardiography, or test form cardiac biomarkers.

Data Collection, Inclusion and Exclusion Criteria

From the case logbooks, signalment such as the gender, age, breed and body weight of the dog was obtained. Based on the case number of dog patients suspected or diagnosed with heart disease was recorded, the files were manually retrieved and examined for data collection. Acquired heart diseases were defined as diseases that are not presented readily at birth. The inclusion criteria of dog patients diagnosed with heart disease were: i) retrievable case file, ii) complete case signalments such as gender, age, breed, and body weight and iii) a confirmed diagnosis of heart disease with available radiographic and echocardiographic images for re-evaluation. Cases with unconfirmed heart diseases i.e., there was no evidence of affirmative echocardiographic, electrocardiography, or test kit results, had non-retrievable case files, or incomplete information was excluded from the study.

Definition of Risk Factors

The dogs were grouped according to their gender, age, and breed size. The gender of the dog is referred to as either male or female without any regard to its neuter status. Age was further defined in three groups; puppy (<1-year-old) and adult (between 1 to 6-year-old) (Kruger et al 2017), and senior (>7-year-old) (Bellows et al. 2015). The breed size of dogs was determined based on American Kennel Club (AKC) classification. When information of breed was available, the body weights and age were used to guestimate the breed size, categorised as small (weight <10kg), medium (weight between 10 to 19kg) and large breed (weight >19kg) (American Kennel Club 2020).

Statistical Analysis

Data were descriptively analysed using Microsoft Excel (2019) and exported to SPSS 26 (Version 26.0, USA) for further analysis. Continuous variables were reported as mean and interquartile range and categorical variables were reported as proportions, expressed in percentage and its 95% confidence interval (CI). The proportion of heart disease cases was calculated by dividing the total number of confirmed heart disease cases by the total number of all cases. Gender, age and breed size were defined as potential risk factors. Logistic regression was carried out to determine the relationship between heart disease and the risk factors. Two models were tested in this study, one involving all of the heart disease cases and secondly, based on the most common heart disease in the population. Dogs with heart disease were made dummy coded as 1. In the overall dog population and the specific heart disease model, female, adult age group, and medium breed size were used as reference. All factors possessing $P<0.05$ after univariate logistic regression were submitted for multiple logistic regression models using a backward likelihood ratio elimination method to obtain the final model. The final model was chosen based on the largest Nagelkerker R2 and the following assumptions were met: (i) Hosmer-Lemeshow test was not significant ($P>0.05$); (ii) overall percentage from classification table >70% and (iii) area under the Receiver Operating Characteristic curve (AUC)

>0.70. Interaction and multi-collinearity were evaluated by determining the variation inflation factors (VIF) <10 before accepting the final model. Statistical significance was determined by a P<0.05.

RESULTS

A total of 9255 canine cases were presented and the majority were male (n=4991, 53.9%, 95% CI: 0.53-0.55), adult age group (n=4056, 45.6%, 95% CI: 0.43-0.45), and small breed size (n=3592, 56.2% 95% CI: 0.38-0.40) dogs. Out of this total, 795 cases were considered for analysis, and 61 (8.0%) dog patients with suspected heart disease were excluded due to insufficient information. In total, 734 dogs had a diagnosis of heart disease based on echocardiography, making the proportion of heart disease patients 7.9% (95% CI: 0.07-0.09). The affected dogs were predominantly male (n=397, 54.1%,95% CI: 0.04-0.05) with a mean age of 9.0 and an interquartile range of 8.0-12.0 years. The senior-aged dogs (n=558, 76.0%, 95% CI: 0.05-0.06) and small breed sizes (n=469, 63.2%, 95% CI: 0.05-0.06) were the most frequently diagnosed. In terms of breeds, Shih Tzu (n=172, 23.4%, 95% CI: 0.02-0.02) were the most frequently affected (Table 1).

There were 31 dogs that had more than one type of heart disease identified at the point of diagnosis, hence the total number of heart diseases diagnosed was 765. Valvular disease was predominant type of heart disease (n=528, 69.0%,95% CI: 0.05-0.06). Congenital disease accounts for a small proportion of the heart disease cases (n=10, 1.3%,95% CI: 0.00-0.00) (Table 2).

There were 532 out of 734 dogs that were presented with heart-related clinical signs (Table 3). Majority of the dogs were presented with clinical signs of coughing (n=517, 97.2%, 95% CI: 0.95-0.98), followed by tachypnoea (n=217, 40.8%, 95% CI: 0.37-0.45) and exercise intolerance (n=102, 19.2%, 95% CI: 0.16-0.23).

There was a significant association between age group and breed size with heart disease (Table 4). However, Hosmer-Lemeshow statistics were significant P=0.05 which indicated poor fit, with a fair AUC of 0.75. The multivariate logistic regression model was statistically significant $\chi2(4) = 583.54$, P<0.001. The model explained 14.4% of the variance in heart disease and correctly classified 92.1% of cases. When adjusted for breed size, senior dogs had the highest risk (OR 3.68, 95% CI: 3.08-4.41; P<0.001) for heart disease.

The following analysis was carried out based on commonly diagnosed acquired heart diseases in the population namely valvular disease, heartworm disease, and DCM (Table 5). There was an association between gender, age group, and breed size with valvular disease in dogs. The multivariate model was statistically significant ($\chi2(4) = 259.5$, P<0.05), explained 40.7% of the variance, and correctly classified 79.9% of cases. Hosmer - Lemeshow test for the model was P=1.00, with an AUC of 0.84. After adjustments with gender and breed size, senior dogs were found to have 3.54 times increased odds for valvular disease compared to adult dogs. Small breed dogs were found to have 6.74 times increased odds for valvular disease.

For heartworm disease, both breed size and age group were important risk factors (P<0.05) (Table 5). The multivariate logistic regression model explained 24.4% of the variance in heart disease and correctly classified 85.6% of cases ($\chi2(4) = 114.1$, P<0.001). Hosmer- Lemeshow test for the model was p= 0.65, with an AUC of 0.78. After adjustments, senior age dogs were 0.29 times less likely to have heartworm disease, and large breed dogs (OR 8.32, 95% CI: 4.68-14.78, P<0.001) are at higher risk of the disease.

Lastly, gender and breed size were shown to have an association with the risk of being diagnosed with DCM (Table 5). The multivariate logistic regression model was statistically significant, $\chi2(4) = 122.5$, P<0.001, explained with 28.0% of the variance and correctly classified 88.1% of cases. Hosmer- Lemeshow test for the model was p= 0.77, with an AUC of 0.82. Male dogs (OR:1.82 95% CI: 1.10-3.02, P=0.02) are riskier for DCM In terms of breed sizes, large breed dogs are more likely to be diagnosed compared to medium breed dogs (OR 3.1, 95% CI: 1.80-5.35, P<0.001).

DISCUSSION

This study provides information on distribution and risk factors of canine heart disease among dogs presented to a veterinary teaching hospital in Peninsular Malaysia from July 2013 to July 2020. In this study, there were 7.9% of dogs diagnosed with heart disease, and this finding was slightly lower compared to previous findings in primary care centres in the United States (Keene et al. 2019). The differences may be due to dissimilarities in inclusion criteria and the number of caseloads. Exclusion of up to 8.0% of suspected cases as a confirmatory diagnosis via echocardiography was not achieved, which might also have affected distribution in this study. To a certain extent, the owner's awareness and knowledge of canine heart disease and the importance of veterinary care may also affect the findings. Locally, a study has shown that pet owners had high awareness about heart disease, however, they lack the ability in recognizing the clinical signs (Khor et al. 2020; Tanweer et al. 2020). Regular check-ups and cardiac screening especially in predisposed breeds allow more preclinical diseases to be detected. However, this practice is not common locally. Therefore, the possibility of underdiagnosis cannot be disregarded.

The majority of the heart diseases diagnosed in this sample population were related to valvular disease. This could be related to the over-presentation of small-breed dogs, as small breeds carried a high predisposition towards the disease. As for heartworm disease, Malaysia is hyperendemic (Chelliah and Šlapeta 2019) and it was not surprising that heartworm disease was ranked second being diagnosed among the dogs in this study. Being a country with a tropical climate, the mosquito is available all year round in Malaysia as the hot and humid weather provides a suitable breeding environment. Local spread of heartworm disease may be attributed to infected stray populations which acted as a reservoir host (Lau 2017). Between year 2017-2018, the prevalence of heartworm disease in Kuala Lumpur was lower at 3.8% and antigen-positive tested dogs have inconsistent prevention (Chelliah and Šlapeta 2019). Monthly administration of macrocyclic lactones and annual testing is the best prophylaxis for the disease besides mosquito control (Nelson et al. 2018). DCM affects

Table 1: Frequency (n), percentage (%), and 95% CI of distribution of heart and non-heart disease dogs presented to the University Veterinary Hospital, Universiti Putra Malaysia (UVH) from July 2013 to July 2020

Profile	Non-heart disease (n=8521)			Heart disease (n=734)			Total (n=9255)		
	n	%	95% CI	n	%	95% CI	n	%	95% CI
Gender									
Male	4594	53.9	0.49-0.51	397	54.1	0.04-0.05	4991	53.9	0.53-0.55
Female	3927	46.1	0.41-0.43	337	45.9	0.04-0.04	4264	46.1	0.45-0.47
Age Group (years)									
Puppy (< 1)	1377	16.2	0.14-0.16	7	1.0	0.00-0.00	1384	15.0	0.14-0.16
Adult (1-6.9)	3887	45.6	0.41-0.43	169	23.0	0.02-0.02	4056	43.8	0.43-0.45
Senior (> 7)	3257	38.2	0.34-0.36	558	76.0	0.06-0.07	3815	41.2	0.40-0.42
Breed Size									
Small	3123	36.0	0.33-0.35	469	63.2	0.05-0.06	3592	38.8	0.38-0.40
Shih tzu	928	10.9	0.09-0.11	172	23.4	0.02-0.02	1100	11.9	0.11-0.13
Poodle	792	9.3	0.08-0.09	59	8.0	0.00-0.01	851	9.2	0.09-0.10
Miniature pinscher	352	4.1	0.03-0.04	38	5.2	0.00-0.01	390	4.2	0.04-0.05
Terrier	168	2.0	0.02-0.02	13	1.8	0.00-0.00	181	2.0	0.02-0.02
Pomeranian	164	1.9	0.02-0.02	37	5.0	0.00-0.01	201	2.2	0.02-0.02
Others	132	1.5	0.01-0.02	44	<1.0	0.00-0.01	176	1.9	0.02-0.02
Silky terrier	98	1.2	0.01-0.01	12	1.6	0.00-0.00	110	1.2	0.01-0.01
Chihuahua	87	1.0	0.01-0.01	11	1.5	0.00-0.00	98	1.1	0.01-0.01
Crossbreeds	86	1.0	0.01-0.01	4	0.5	0.00-0.00	90	1.0	0.01-0.01
Spitz	86	1.0	0.01-0.01	13	1.8	0.00-0.00	99	1.1	0.01-0.01
Pekingese	76	0.9	0.01-0.01	18	2.5	0.00-0.00	94	1.0	0.01-0.01
Pug	63	0.7	0.01-0.01	7	1.0	0.00-0.00	70	0.8	0.01-.0.01
Maltese	56	0.7	0.00-0.01	18	2.6	0.00-0.00	74	0.8	0.01-0.01
Cavalier King Charles Spaniel	11	0.1	0.00-0.00	3	0.4	0.00-0.00	14	0.2	0.00-0.00
Papillon	8	0.1	0.00-0.00	1	0.1	0.00-0.00	9	0.1	0.00-0.00
Miniature schnauzer	8	0.5	0.00-0.00	41	5.6	0.00-0.01	49	0.5	0.00-0.01
Bichon frise	5	0.05	0.00-0.00	1	0.1	0.00-0.00	6	0.06	0.00-0.00
Lhasa apso	3	0.03	0.00-0.00	1	0.1	0.00-0.00	4	0.04	0.00-0.00
Tibetan spaniel	-	-	-	2	0.3	0.00-0.00	2	0.02	0.00-0.00
Medium	3204	7.8	0.34-0.36	178	26.7	0.02-0.02	3382	36.5	0.36-0.38
Local (mongrel)	2558	30.0	0.27-0.29	105	14.3	0.01-0.01	2663	28.8	0.28-0.30
Beagle	166	1.9	0.02-0.02	13	1.8	0.00-0.00	179	1.9	0.02-0.02
Cocker Spaniel	112	1.3	0.01-0.01	38	5.2	0.00-0.01	150	1.6	0.01-0.02
Crossbreeds	130	1.5	0.01-0.02	4	0.5	0.00-0.00	134	1.5	0.01-0.02
Others	57	<1.0	0.00-0.01	25	<1.0	0.00-0.00	82	0.9	0.01-0.01
Bulldog	75	0.9	0.01-0.01	4	0.5	0.00-0.00	79	0.9	0.01-0.01
Chow chow	24	0.3	0.00-0.00	2	0.3	0.00-0.00	26	0.3	0.00-0.00
Border collie	23	0.3	0.00-0.00	2	0.3	0.00-0.00	25	0.3	0.00-0.00
Springer Spaniel	18	0.2	0.00-0.00	3	0.4	0.00-0.00	21	0.2	0.00-0.00
Pitbull	20	0.2	0.00-0.00	1	0.1	0.00-0.00	21	0.2	0.00-0.00
Basset hound	15	0.2	0.00-0.00	1	0.1	0.00-0.00	16	0.2	0.00-0.00
Shiba inu	6	0.07	0.00-0.00	1	0.1	0.00-0.00	7	0.08	0.00-0.00
Bull terrier	-	-	-	3	0.4	0.00-0.00	3	0.03	0.00-0.00
Large	2194	56.2	0.23-0.25	87	11.9	0.01-0.01	2281	24.7	0.24-0.26
German Shepherd	467	5.5	0.05-0.06	10	1.4	0.00-0.00	477	5.2	0.05-0.06
Rottweiler	394	4.6	0.04-0.05	13	1.8	0.00-0.00	407	4.4	0.04-0.05
Golden Retriever	386	4.5	0.04-0.05	14	1.9	0.00-0.00	400	4.3	0.04-0.05
Labrador	303	3.6	0.03-0.04	17	2.3	0.00-0.00	320	3.5	0.03-0.04
Others	163	<1.0	0.02-0.02	21	<1.0	0.00-0.00	184	2.0	0.02-0.02
Siberian Husky	155	1.8	0.01-0.02	1	0.1	0.00-0.00	156	1.7	0.01-0.02
Doberman	98	1.2	0.01-0.01	12	1.6	0.00-0.00	110	1.2	0.01-0.01
Crossbreeds	66	0.8	0.01-0.01	4	0.5	0.00-0.00	70	0.8	0.01-0.01
Malinois	60	0.7	0.01-0.01	1	0.1	0.00-0.00	61	0.7	0.01-0.01
Dalmatian	32	0.4	0.00-0.00	7	1.0	0.00-0.00	39	0.4	0.00-0.01
Mastiff	36	0.4	0.00-0.01	2	0.3	0.00-0.00	38	0.4	0.00-0.01
Boxer	18	0.2	0.00-0.00	3	0.4	0.00-0.00	21	0.2	0.00-0.00
Alaskan Malamute	13	0.15	0.00-0.00	1	0.1	0.00-0.00	14	0.2	0.00-0.00
Boerboel	2	0.02	0.00-0.00	1	0.1	0.00-0.00	3	0.03	0.00-0.00
Afghan Hound	1	0.01	0.00-0.00	1	0.1	0.00-0.00	2	0.02	0.00-0.00

approximately 0.1% of dogs in the United States, and 1.1% in Europe (Fioretti and Delli 1988). A retrospective study in Kuala Lumpur from 2015 to 2017 revealed that 6.49% of the heart disease cases were DCM, preceded by valvular disease (Yap et al. 2021). The distribution of DCM cases was slightly higher in this study, most likely due to a longer inclusion period (7 years) and caseload difference. However, the possibility of increased diagnosis in recent years secondary to nutritional causes, cannot be disregarded.

Clinical signs shown by dogs with heart disease are related to congestive heart failure (CHF). Depending on the type of heart disease, CHF may be caused by high venous pressure (backward failure) or the inability of the heart to pump adequate output (forward failure) (Nelson and Couto

Table 2: The different types of heart disease diagnosed among the heart disease cases (n=765) presented to the University Veterinary Hospital, Universiti Putra Malaysia (UVH) from July 2013 to July 2020

Type of disease	Diseases	Frequency (n)	Percentage (%)	95% CI
Acquired	Valvular	528	69.0	0.05-0.06
	Mitral valve	291	38.0	0.03-0.04
	Tricuspid valve	8	1.0	0.00-0.00
	Mitral and tricuspid	229	29.9	0.02-0.03
	Heartworm disease	113	14.8	0.01-0.01
	Dilated cardiomyopathy	90	11.6	0.01-0.01
	Pericardial effusion	5	0.7	0.00-0.00
	Arrythmogenic right ventricular cardiomyopathy	4	0.5	0.00-0.00
	Tumour	4	0.5	0.00-0.00
	Endocarditis	4	0.5	0.00-0.00
	Hypertrophic cardiomyopathy	3	0.4	0.00-0.00
	Pulmonary hypertension	3	0.4	0.00-0.00
	Sick sinus syndrome	1	0.1	0.00-0.00
Congenital	Patent ductus arteriosus	5	0.6	0.00-0.00
	Interventricular septal disease	3	0.2	0.00-0.00
	Subaortic stenosis	1	0.1	0.00-0.00
	Mitral valve dysplasia	1	0.1	0.00-0.00

Table 3: Frequency (n), percentage (%), and 95% CI of distribution of clinical signs related to heart disease shown by dogs (n=532) presented to the University Veterinary Hospital (UVH) Universiti Putra Malaysia from July 2013 to July 2020

Clinical signs	Frequency (n)	*Percentage (%)	95% CI
Coughing	517	97.2	0.95-0.98
Tachypnoea	217	40.8	0.37-0.45
Exercise intolerance	102	19.2	0.16-0.23
Lethargy	158	29.7	0.26-0.34
Syncope	42	7.9	0.06-0.10
Inactivity	27	5.1	0.04-0.07
Dyspnoea	132	24.8	0.21-0.29
Abdominal breathing	13	2.4	0.01-0.04
Inappetence	11	2.1	0.01-0.04
Anasarca	2	0.4	0.00-0.01

Notes: * - total unequal to 100% because a case may show more than one clinical sign

Table 4: Univariate and multivariable logistic regression analyses between risk factors (gender, age group, and breed size) and heart disease in 9255 dogs presented to the University Veterinary Hospital, Universiti Putra Malaysia (UVH) between July 2013 and July 2020

Factors	Total cases	Heart disease cases (n)	Percentage (%)	χ^2	P value	Univariate Logistic Regression			Multivariate Logistic Regression		
						β	Crude OR (95% CI)	P value	β	Adjusted OR (95% CI)	P value
Gender				0.008	0.93						
Female	4264	337	7.9				Ref		-	-	-
Male	4991	397	8.0			-0.007	1.00 (0.57-1.16)	0.93	-	-	-
Age group				416.28	<0.001*						
Adult	4056	169	2.0				Ref		-	Ref	-
Senior	3815	558	14.6			1.37	3.93 (3.29-4.70)	<0.001	1.30	3.68 (3.08-4.41)	<0.001*
Puppy	1384	7	0.5			-2.15	0.12 (0.06-0.25)	<0.001	-2.05	0.13 (0.06-0.28)	<0.001*
Breed size				189.31	<0.001*						
Medium	2282	87	3.8				Ref		-	Ref	-
Small	3581	469	13.0			0.89	2.43 (2.04-2.90)	<0.001	0.63	1.87 (1.57-2.24)	<0.001*
Large	3392	178	5.2			-0.41	0.66 (0.51-0.86)	0.002*	-0.54	0.58 (0.45-0.76)	<0.001*

χ^2=Pearson chi-square, n=number; β=unstandardized regression coefficient; OR: odds ratio, CI: Confidence interval, Ref: reference; *P<0.05

2014). Coughing is presented in the majority of canine heart disease patients (Chetboul et al. 2017; Martin et al. 2009) and was speculated due to mechanical pressure on main stem bronchus due to left atrial enlargement and exacerbated by airway disease especially in older dogs (Ferasin et al. 2013) and/or triggered by a fulminant cardiogenic pulmonary oedema (Ferasin and Linney 2019). Breathing disturbances such as dyspnoea are often seen secondary to cardiogenic pulmonary oedema (Tilley et al. 2008) secondary to backward failure.

The model for overall heart disease risk has fair predictive power, however, its goodness-of-fit is poor. The model did not properly match to the distribution of actual events of canine heart disease in the sample population, suggesting that there may be other important risk factors that were not explored in this study. Gender as a significant risk factor was only seen in both the valvular disease and DCM. Previous findings had shown certain breeds such as Cavalier King Charles Spaniel and Dachshunds (Thrusfield et al. 1985; Andrei and Vulpe 2021) and especially male dogs were riskier for valvular disease, despite its exact cause being unclear (Mattin et al. 2015). In contrast, a retrospective study with a heterogeneous mix of breeds found that there was no significant difference between the distribution of valvular disease between male and female dogs (Kim et al. 2017). In this study, however, it was found that female dogs were at higher risk of the disease in contrast with previous findings. Primary mitral valve

Table 5: Univariate and multivariable logistic regression analyses between risk factors (gender, age group, and breed size) and valvular disease, heartworm disease, and dilated cardiomyopathy in 9255 dogs presented to the University Veterinary Hospital, Universiti Putra Malaysia (UVH) between July 2013 and July 2020

Heart Disease	Factors	Total dogs (n)	Diseased cases (n)	Percentage (%)	χ^2	P value	β	Crude OR (95% CI)	P value	β	Adjusted OR (95% CI)	P value
Valvular	**Gender**				4.39	0.04*						
Disease	Female	4280	257	5.9				Ref			Ref	
(n=528)	Male	5006	271	5.4			-0.33	0.72 (0.53-0.98)	0.04*	-0.49	0.61 (0.41-0.90)	0.01*
	Age group				70.93	<0.001*						
	Adult	3838	83	11.4				Ref			Ref	
	Senior	4064	445	2.0			1.31	3.70 (2.60-5.24)	<0.001*	1.91	3.54 (2.32-5.37)	<0.001*
	Puppy	1384	0	0.0			-21.0	0.00 (0.00-NA)	1.0	-21.3	0.00 (0.00-NA)	1.00
	Breed size				221.12	<0.001*						
	Medium	2288	95	17.9				Ref			Ref	
	Small	3607	416	2.6			1.88	6.54 (4.46-9.60)	<0.001*	1.91	6.74 (4.51-10.1)	<0.001*
	Large	2291	17	0.7			-1.56	0.21 (0.12-0.34)		-1.55	0.22 (0.12-0.40)	<0.001*
Heartworm	**Gender**				2.77	0.10						
Disease	Female	4280	44	1.0				Ref		-	-	-
(n=113)	Male	5006	69	1.4			0.35	1.41 (0.94-2.13)	0.10	-	-	-
	Age group				51.21	<0.001*						
	Adult	3838	56	1.5				Ref			Ref	
	Senior	4064	54	1.3			-1.41	0.24 (0.16-0.37)	<0.001*	-1.24	0.29 (0.19-0.46)	<0.001*
	Puppy	1384	3	0.2			0.54	1.71 (0.40-7.90)	0.50	0.80	2.20 (0.40-12.23)	0.36
	Breed size				84.23	<0.001*						
	Small	3607	27	0.7				Ref			Ref	
	Medium	2288	54	2.4			1.87	6.46 (3.92-10.64)	<0.001*	-1.81	6.11 (3.66-10.20)	<0.001*
	Large	2291	32	1.4			2.11	8.32 (4.68-14.78)	<0.001*	2.00	7.18 (4.00-13.01)	<0.001*
DCM	**Gender**				5.62	0.018*						
(n=90)	Female	4280	31	0.7				Ref			Ref	
	Male	5006	59	1.2			0.55	1.74 (1.10-2.75)	0.02*	0.61	1.83 (1.11-3.04)	0.02*
	Age group				0.07	0.16						
	Adult	3838	27	1.6				Ref			-	-
	Senior	4064	63	0.7			-0.41	0.10 (0.67-1.08)	0.10		-	-
	Puppy	1384	0	0.0			19.50	0.00 (0.00-NA)	1.0		-	-
	Breed size				130.31	<0.001*						
	Medium	2288	37	1.6				Ref			Ref	
	Small	3607	13	0.4			-2.13	0.12 (0.06-0.23)	<0.001*	-2.13	0.12 (0.06-0.23)	<0.001*
	Large	2291	40	1.7			1.10	3.01 (1.75-5.16)	<0.001*	1.14	3.12 (1.80-5.39)	<0.001*

DCM=Dilated cardiomyopathy, χ^2=Pearson chi-square, n=number; β=unstandardized regression coefficient; OR=odds ratio, CI=Confidence interval, Ref=reference; *P<0.05.

disease in humans bears resemblance in terms of pathology with the valvular disease in dogs. In humans, the prevalence and risk of mitral valvular disease are higher among women, with more extensive lesions with remarkable extreme gross valvular changes (Avierinos et al. 2002). The exact aetiology remains unknown; however, it was speculated to be related to different stresses acquired throughout life such as pregnancies and fluctuating levels of cardioprotective oestrogen (Youssef 2021). The role of oestrogen in the cardiovascular system of dogs however was unclear, while inconsistent findings on changes in the level of heart rate, cardiac output level, and echocardiographic findings during pregnancy made the exact role of hemodynamic stress on the risk of heart disease in dogs remains unclear (Brooks and Keil 1994; Olsson et al. 2003; Abbott 2010; Blanco et al. 2011; de Souza et al. 2017; Ward et al. 2020). However, in neutered dogs, although other cardiac parameters were indifferent, higher blood triglyceride (TG) and very-low-density lipoprotein (vLDL) was found compared to intact dogs, implying the lost role of oestrogen in the synthesis of anti-oxidant and atherosclerosis-preventing high-density lipoprotein (HDL) (Boonyapakorn et al. 2020). Despite not being a major concern among dogs, atherosclerosis may affect vascular distensibility and increase vascular resistance, which chronically, may pose additional pressure on the heart. Neutered females were reported to have a longer lifespan (O'Neill et al. 2013). which then may have allowed valve lesions to advance to the chronic stage, resulting in clinical signs of congestive heart failure. In this study, the neuter status among dogs was not considered for analysis due to inconsistent reporting in the case file. Therefore, dogs included in the study were a heterogeneous mix of neutered and non-neutered dogs, which may influence the findings. Incidentally in this population, slightly more males were found to have both mitral and tricuspid affected compared to females, however, this finding was not statistically significant.

Similar to the findings of this study, DCM is typically more prevalent among males (Tilley et al. 2008). The link between gender and predisposition to DCM is still unclear, though the hereditary risk may be one of the possible causes in certain breeds. In Great Danes for example, the X-linked recessive trait (Meurs et al. 2001) may cause the disease to be more presented among males. However, in this study, most of the DCM dogs were either Local or Labrador, which is not known to carry these hereditary risks. Therefore, further study with emphasis on the role of dogs in the population and may help to better elucidate this finding. In terms of breed sizes, small breed dogs have a higher risk of valvular disease. The valvular disease may have genetic involvement, particularly due to alterations in genes controlling body size and heart development (Jones et al. 2008), and in combination with the genes related to the composition of materials important for valve structure and maintenance such as collagen, proteoglycan, and hyaluronan (Madsen et al. 2011). A single nucleotide polymorphism (SNP) allele frequencies comparison in small breed dogs revealed a selective sweep spanning of insulin growth factor (IGF1), a gene responsible for body size (Sutter et al. 2007), and cardiac development (Donath et al. 1994) which is shared across multiple breeds.

In this study, 176 (23.0%) of heart disease cases were Shih Tzus, with 161 (91.5%) of them being diagnosed with valvular disease. The distribution of valvular disease among Shih Tzus in this population is 17.1%. Previous studies revealed that Shih Tzus had higher risk of cardiovascular disease (Inoue et al. 2016) and were especially predisposed to valvular diseases (Serfass et al. 2006; Mattin et al. 2015). It was speculated that the small breed dogs may have shared common ancestors that carried the disease, and hence reduction in gene pools may be contributed to more apparent disease among the recent generation of dogs. Shih Tzus may have obtained their share of the disease through genomes from the Modern cluster (Parker 2012). A further breed-specific study in affected Shih Tzus and identifying the genetic component locally may be beneficial.

This study found that the large breed dogs had a higher risk of heartworm disease, presumably related to dogs being housed in the outdoor kennel which may expose the dog to mosquitoes, or lack of constant preventative measures. Similarly, large breed dogs have a higher risk for DCM. Hereditary risk of DCM had been observed among certain large breed dogs due to splice site mutation, such as Doberman Pinschers on pyruvate dehydrogenase kinase 4 (PDK4) gene (Meurs et al. 2012), Boxers due to Striatin (STRN) gene (Meurs et al. 2013), Irish Wolfhounds due to polymorphisms on chromosomes 1, 10, 15, 17, and 21 (Philipp et al. 2012) and due to X-linked recessive trait such as in Great Danes (Meurs et al. 2001). In this study, the local breed, followed by Labradors were most affected with DCM. The genetic cause may be possible in the local breed due to long lines of crossbreeding (Boyko et al. 2010), however, diet may also play a role. In recent years, nutrition had been re-speculated to be the cause particularly grain-free diets that may cause reversible DCM among non-predisposed breeds (Adin et al. 2020; Ontiveros et al. 2020). Other than that, homecooked diets which may be popular among local dog owners may have resulted in DCM secondary to taurine deficiency. Anecdotally, veterinarians revealed that it was common among dog owners to mix both homecooked food and commercial feeds in smaller proportions. It was being informed that dog owners perceived that feeding cooked meat with adequate protein and vegetables is a better option of healthier food and a more convenient option for salt controlled diet (for dogs diagnosed with heart disease). Hence, getting information on the dietary intakes among local and Labrador breeds locally may be necessary to better understand the high DCM occurrence.

A higher risk of heart disease was seen among older-aged dogs. Age-related changes to the canine cardiovascular system may include decline to beta-adrenergic stimulation (Yin et al. 1979), functional changes to the catecholaminergic system which caused progressive loss of organ reserve and adaptability (Strasser et al. 1997), and higher pulmonary arterial pressure due to high pulmonary vascular resistance (Mercier et al. 2010). The exact role of these age-related changes in the pathophysiology of heart disease in dogs is yet to be ascertained. As these changes occur due to cellular inefficiency in maintenance, repair, and turnover pathways at molecular levels (Holliday 1995), it is theoretically possible that it contributes to functional inefficiency. Age-related changes of other systems such as renal and hepatic may also predispose or exacerbate senior-aged dogs to heart disease (Saunders 2012). Similarly, senior-aged dogs have a higher risk of valvular disease, similar to previous findings (Mattin et al. 2015). Older dogs were found to have a progressive decrease in the number of valve endothelial cells, increase in valvular interstitial cells, decreased innervation, and decreased elastin (Aupperle and Disatian 2012), which may have contributed to poor maintenance of the valvular structure. In CDVD, gross lesion severity increases with age (Whitney 1974) except for the predisposed breeds. Valvular diseases have a long preclinical period and clinical signs may take time to appear (Urfer et al. 2017), therefore it may be common for most of the diagnoses to be made at later stages of life. In contrast, this study found that senior-aged dogs have a lower risk of heartworm. Increased frequency to veterinary clinics due to geriatric disease may have opened up the opportunity for the reminder to screen and initiate heartworm prevention among senior dogs, hence the lower risk of the disease among this age subgroup.

Information from this study should be interpreted with caution due to some limitations. All the dogs diagnosed with heart disease were patients from a veterinary teaching hospital which were mainly from Klang Valley and a small percentage came from other states. Other risk factors such as heartworm prevention compliance, management, the role of the dogs (i.e., working and non-working), and dietary aspects which may also influence the risk of heart disease, was not covered in this study.

Conclusion

The valvular disease is the most commonly diagnosed heart disease in UVH. Age, breed size and gender play important roles in the occurrence of heart diseases in dogs. The study findings may be used by clinicians to improve clinical diagnosis, management, and provide a prognosis for cases of canine heart disease. This study also provides the baseline information needed for future studies on local healthcare facilities and the need for early screening for heart disease in dogs and should be advocated especially in the geriatric age group of dogs.

Acknowledgement

We thank the administrators of UVH for permission to conduct the study and especially staff from the Reception Counter for providing assistance during the period of data collection, as every case file were manually retrieved. We also thank the staffs of UVH, particularly from Diagnostic

Imaging Unit for their help in accessing the necessary imaging files.

Abbreviations

AKC: American Kennel Club
AUC: Area under Receiver Operating Curve
CDVD: Chronic degenerative valvular disease
DCM: Dilated cardiomyopathy
HDL: High density lipoprotein
PDK: Pyruvate dehydrogenase kinase 4 (PDK4)
SNP: Single nucleotide polymorphism
STRTN: Striatin gene
UVH: University Veterinary Hospital
VHS: Vertebral heart score
VIF: Variance inflation factor
vLDL: Very low-density lipoprotein

Authors' Contribution

Research was designed by Khor Kuan Hua, data collection was conducted by Norhidayah Noordin and Ee Kai Lee, data analysis was carried out by Norhidayah Noordin, Ee Kai Lee, Khor Kuan Hua, and Siti Zubaidah Ramanoon. Manuscript preparation was done by Norhidayah Noordin, Khor Kuan Hua, Siti Zubaidah Ramanoon and Lau Seng Fong.

REFERENCES

Abbott JA, 2010. The effect of pregnancy on echocardiographic variables in healthy bitches. Journal of Veterinary Cardiology 12: 123–128. https://doi.org/10.1016/J.JVC.2010.02.001

Adin D, Kurtz K, Atkins C, Papich MG and Vaden S, 2020. Role of electrolyte concentrations and renin-angiotensin-aldosterone activation in the staging of canine heart disease. Journal of Veterinary Internal Medicine 34: 53–64. https://doi.org/10.1111/jvim.15662

American Kennel Club Retrieved July 1, 2020, from https://www.akc.org/

Andrei B and Vulpe V, 2021. Prevalence of cardiac diseases in small animals: A five-year single-center retrospective study https://www.researchgate.net/publication/352998706

Aupperle H and Disatian S 2012. Pathology, protein expression and signaling in myxomatous mitral valve degeneration: Comparison of dogs and humans. Journal of Veterinary Cardiology 14: 59–71. https://doi.org/10.1016/j.jvc. 2012.01.005

Avierinos JF, Gersh BJ, Melton LJ, Bailey KR, Shub C, Nishimura RA, Tajik AJ and Enriquez-Sarano M, 2002. Natural history of asymptomatic mitral valve prolapse in the community. Circulation 106: 1355–1361. https://doi.org/10.1161/01.cir.0000028933.34260.09

Bellows J, Colitz CMH, Daristotle L, Ingram DK, Lepine A, Marks SL, Sanderson SL, Tomlinson J and Zhang J, 2015. Common physical and functional changes associated with aging in dogs. Journal of the American Veterinary Medical Association 246: 67–75. https://doi.org/10.2460/javma.246.1.67

Blanco PG, Tórtora M, Rodriguez R, Arias DO and Gobello C, 2011. Ultrasonographic assessment of maternal cardiac function and peripheral circulation during normal gestation in dogs. The Veterinary Journal 190: 154–159. https://doi.org/10.1016/j.tvjl.2010.08.01

Boonyapakorn C, Punyapornwithaya V, Sawatphakdee G, Poolsawat N and Pongkan W, 2020. Estrogen deprivation induces lipid profile impairment but not cardiac dysfunction in ovariohysterectomized dogs. Polish Journal of Veterinary Sciences 23: 521–528. https://doi.org/10.24425/pjvs.2020.134701

Borgarelli M and Buchanan JW, 2012. Historical review, epidemiology and natural history of degenerative mitral valve disease. Journal of Veterinary Cardiology 14: 93–101. https://doi.org/10.1016/j.jvc.2012.01.011

Boyko AR, Quignon P, Li L, Schoenebeck JJ and Degenhardt JD, 2010. A simple genetic architecture underlies morphological variation in dogs. PLoS Biology 8: 1000451. https://doi.org/10.1371/journal.pbio.1000451

Brambilla PG, Polli M, Pradelli D, Papa M, Rizzi R, Bagardi M and Bussadori C, 2020. Epidemiological study of congenital heart diseases in dogs: Prevalence, popularity, and volatility throughout twenty years of clinical practice. PLoS One 15: e0230160. https://doi.org/10.1371/journal.pone.0230160

Brooks VL and Keil LC, 1994. Changes in the baroreflex during pregnancy in conscious dogs: heart rate and hormonal responses. Endocrinology 135: 1894–1901. https://doi.org/10.1210/endo.135.5.7956910

Buchanan JW, 1977. Chronic valvular disease (endocardiosis) in dogs. Advances in Veterinary Science and Comparative Medicine 21: 75–106.

Chetboul V, Pouchelon JL, Menard J, Blanc J, Desquilbet L, Petit A, Rougier S, Lucats L and Woehrle F, 2017. Short-term efficacy and safety of torasemide and furosemide in 366 dogs with degenerative mitral valve disease: The TEST study. Journal of Veterinary Internal Medicine 31: 1629–1642. https://doi.org/10.1111/jvim.14841

Chetboul V, Tissier R, Villaret F, Nicolle A, Déan E, Benalloul T and Pouchelon JL, 2004. Caractéristiques épidémiologiques, cliniques, écho-doppler de l'endocardiose mitrale chez le Cavalier King Charles en France: étude retrospective de 451 cas (1995 à 2003). The Canadian Veterinary Journal 45: 1012.

Chelliah KM and Šlapeta J, 2019. The prevalence and trends of canine heartworm *(Dirofilaria immitis*) in Kuala Lumpur, Malaysia (1970-2018). Veterinary Parasitology: Regional Studies and Reports 2019: 100272. https://doi.org/10.1016/j.vprsr.2019.100272

de Souza RCA, Peres R, Sousa MG and Camacho AA, 2017. Cardiac parameters during the estrous cycle of canine bitches. Pesquisa Veterinária Brasileira 37: 295–299.

Detweiler DK and Patterson DF, 1965. The prevalence and types of cardiovascular disease in dogs. Annals of the New York Academy of Sciences 127: 481–516. https://doi.org/10.1111/J.1749-6632.1965.tb49421.X

Donath MY, Zapf J, Eppenberger-Eberhardtt M, Froesch ER and Eppenbergert HM, 1994. Insulin-like growth factor I stimulates myofibril development and decreases smooth muscle a-actin of adult cardiomyocytes (heart/hypertrophy/type 1 insulin-like growth factor receptor). Medical Sciences 91: 1686–1690.

Egenvall A, Bonnett BN, Hedhammar Å and Olson P, 2005. Mortality in over 350,000 insured Swedish dogs from 1995-2000: II. Breed-specific age and survival patterns and relative risk for causes of death. Acta Veterinaria Scandinavica 46: 121–136. https://doi.org/10.1186/1751-0147-46-121

Ferasin L, Crews L, Biller DS, Lamb KE and Borgarelli M, 2013. Risk factors for coughing in dogs with naturally acquired myxomatous mitral valve disease. Journal of Veterinary Internal Medicine 27: 286-292. https://doi.org/10.1111/jvim.12039

Ferasin L and Linney C, 2019. Coughing in dogs: what is the evidence for and against a cardiac cough? Journal of Small Animal Practice 60: 139–145. https://doi.org/10.1111/jsap.12976

Fioretti M and Delli C, 1988. Epidemiological survey of dilatative cardiomyopathy in dogs. Veterinaria 2: 1.

Freeman LM, Stern JA, Fries R, Adin DB and Rush JE, 2018. Diet-associated dilated cardiomyopathy in dogs: what do we know? Journal of the American Veterinary Medical Association 253: 1390–1394. https://doi.org/10.2460/javma.253.11.1390

Haritha SG, 2020. Pericardial effusion in dogs. In: Veterinary Medicine and Pharmaceuticals, Bekoe SO, Saravanan M, Adosraku RK and Ramkumar PK (eds). Intech Open Book Series, pp: 787-845. https://doi.org/10.5772/intechopen.89051

Holliday R, 1995. Understanding ageing. Philosophical transactions of the Royal Society of London: Series B, Biological Sciences 352: 1793–1797. https://doi.org/10.1098/rstb.1997.0163

Inoue M, Hasegawa A, Hosoi Y and Sugiura K, 2016. Association between breed, gender and age in relation to cardiovascular disorders in insured dogs in Japan. Journal of Veterinary Medical Science 78: 347–350. https://doi.org/10.1292/jvms.15-0171

Jones P, Chase K, Martin A, Davern P, Ostrander EA and Lark KG, 2008. Single-nucleotide-polymorphism-based association mapping of dog stereotypes. Genetics 179: 1033–1044. https://doi.org/10.1534/genetics.108.087866

Keene BW, Atkins CE, Bonagura JD, Fox PR, Häggström J, Fuentes VL, Oyama MA, Rush JE, Stepien R and Uechi M, 2019. ACVIM consensus guidelines for the diagnosis and treatment of myxomatous mitral valve disease in dogs. Journal of Veterinary Internal Medicine 33: 1127–1140. https://doi.org/10.1111/jvim.15488

Khor KH, Khor KS, Lee YC and Lim JY, 2020. Would Cat Owners Intend to Treat their Cats If Diagnosed with Heart Disease? Journal of Veterinary Behavior 41: 39–46. https://doi.org/10.1016/j.jveb.2020.05.014

Kim HT, Han SM, Song WJ, Kim B, Choi M, Yoon J and Youn HY, 2017. Retrospective study of degenerative mitral valve disease in small-breed dogs: survival and prognostic variables. Journal of Veterinary Science 18: 369–376. https://doi.org/10.4142/jvs.2017.18.3.369

Kruger K, Mccune S and Merrill R, 2017. WALTHAM® Pocket Book of Human-Animal Interactions, Sleek Creative, Leicestershore, United Kingdom, pp: 16.

Lau SF, 2017. Canine vector borne diseases of zoonotic concern in three dog shelters in Peninsular Malaysia: The importance of preventive measures. Tropical Biomedicine 34: 72–79.

Madsen MB, Olsen LH, Häggström J, Höglund K, Ljungvall I, Falk T, Wess G, Stephenson H, Dukes-McEwan J, Chetboul V, Gouni V, Proschowsky HF, Cirera S, Karlskov-Mortensen P and Fredholm M, 2011. Identification of 2 loci associated with development of myxomatous mitral valve disease in Cavalier King Charles Spaniels. The Journal of Heredity 2011 (102 S1): S62–S67. https://doi.org/10.1093/jhered/esr041

Martin MWS, Stafford Johnson MJ and Celona B, 2009. Canine dilated cardiomyopathy: a retrospective study of signalment, presentation and clinical findings in 369 cases. Journal of Small Animal Practice 50: 23–29. https://doi.org/10.1111/J.1748-5827.2008.00659.x

Mattin MJ, Boswood A, Church DB, L Opez-Alvarez J, Mcgreevy PD, O'neill DG, Thomson PC and Brodbelt DC, 2015. Prevalence of and risk factors for degenerative mitral valve disease in dogs. Attending Primary-care Veterinary Practices in England. https://doi.org/10.1111/ jvim.12591

Mercier E, Mathieu M, Sandersen CF, Delvaux FH, Clercx CM and Mc Entee K, 2010. Evaluation of the influence of age on pulmonary arterial pressure by use of right ventricular catheterization, pulsed-wave doppler echocardiography, and pulsed-wave tissue doppler imaging in healthy Beagles. American Journal of Veterinary Research 71: 891–897. https://doi.org/10.2460/ajvr.71.8.891

Meurs KM, Lahmers S, Keene BW, White SN, Oyama MA, Mauceli E and Lindblad-Toh K, 2012. A splice site mutation in a gene encoding for PDK4, a mitochondrial protein, is associated with the development of dilated cardiomyopathy in the Doberman pinscher. Human Genetics 131: 1319–1325. https://doi.org/10.1007/s00439-012-1158-2

Meurs KM, Miller MW and Wright NA, 2001. Clinical features of dilated cardiomyopathy in Great Danes and results of a pedigree analysis: 17 cases (1990-2000). Journal of the American Veterinary Medical Association 218: 729–732. https://doi.org/10.2460/javma.2001.218.729

Meurs KM, Stern JA, Sisson DD, Kittleson MD, Cunningham SM, Ames MK, Atkins CE, Defrancesco T, Hodge TE, Keene BW, Reina Doreste Y, Leuthy M, Motsinger-Reif AA and Tou SP, 2013. Association of dilated cardiomyopathy with the striatin mutation genotype in boxer dogs. Journal of Veterinary Internal Medicine 27: 1437–1440. https://doi.org/10.1111/jvim.12163

Nelson CT, McCall JW, Jones S and Moorhead A, 2018.Current Canine Guidelines for the Diagnosis, Prevention, and Management of Heartworm (*Dirofilaria immitis*) Infection in Dogs. American Heartworm Society, pp: 1-35.

Nelson RW and Couto GC, 2014. Small Animal Internal Medicine, 5th Ed. Elsevier Inc., Missouri, USA, pp: 1

O'Neill DG, Church DB, McGreevy PD, Thomson PC and Brodbelt DC, 2013. Longevity and mortality of owned dogs in England. Veterinary Journal 198: 638–643. https://doi.org/10.1016/j.tvjl.2013.09.020

Oliveira P, Domenech O, Silva J, Vannini S, Bussadori R and Bussadori C, 2011. Retrospective review of congenital heart disease in 976 dogs. Journal of Veterinary Internal Medicine 25: 477–483. https://doi.org/10.1111/J.1939-1676.2011.0711.X

Olsen LH, Fredholm M and Pedersen HD, 1999. Epidemiology and inheritance of mitral valve prolapse in Dachshunds. Journal of Veterinary Internal Medicine 13: 448–456. https://doi.org/10.1111/J.1939-1676.1999.tb01462.x

Olsson K, Lagerstedt AS, Bergström A and Häggström J, 2003. Change of Diurnal Heart Rate Patterns During Pregnancy and Lactation in Dogs (Canis familiaris). Acta Veterinaria Scandinavica 44: 105. https://doi.org/10.1186/1751-0147-44-105

Ontiveros ES, Whelchel BD, Yu J, Kaplan JL, Sharpe AN, Fousse SL, Crofton AE, Fascetti AJ and Stern JA, 2020. Development of plasma and whole blood taurine reference ranges and identification of dietary features associated with taurine deficiency and dilated cardiomyopathy in golden retrievers: A prospective, observational study. PloS One 15. https://doi.org/10.1371/journal.pone.0233206

Parker HG, 2012. Genomic analyses of modern dog breeds 23: 19–27. https://doi.org/10.1007/s00335-011-9387-6

Philipp U, Vollmar A, Häggström J, Thomas A and Distl O, 2012. Multiple Loci Are Associated with Dilated Cardiomyopathy in Irish Wolfhounds. PLOS ONE 7: e36691. https://doi.org/10.1371/journal.pone.0036691

Saunders AB, 2012. The diagnosis and management of age-related veterinary cardiovascular disease. The Veterinary Clinics of North America. Small Animal Practice 42: 655–668. https://doi.org/10.1016/j.cvsm.2012.04.005

Schrope DP, 2015. Prevalence of congenital heart disease in 76,301 mixed-breed dogs and 57,025 mixed-breed cats. Journal of Veterinary Cardiology 17: 192–202. https://doi.org/10.1016/j.jvc.2015.06.001

Serfass P, Chetboul V, Sampedrano CC, Nicolle A, Benalloul T, Laforge H, Gau C, Hébert C, Pouchelon JL and 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: 11–18. https://doi.org/10.1016/j.jvc.2005.10.001

Simón F, Siles-Lucas M, Morchón R, González-Miguel J, Mellado I, Carretón E and Montoya-Alonso JA, 2012. Human and animal dirofilariasis: the emergence of a zoonotic mosaic. Clinical Microbiology Reviews 25: 507. https://doi.org/10.1128/cmr.00012-12

Stephenson HM, Fonfara S, López-Alvarez J, Cripps P and Dukes-McEwan J, 2012. Screening for dilated cardiomyopathy in great danes in the United Kingdom. Journal of Veterinary Internal Medicine 26: 1140–1147. https://doi.org/10.1111/J.1939-1676.2012.00987.X

Strasser A, Simunek M, Seiser M and Hofecker G, 1997. Age-dependent changes in cardiovascular and metabolic responses to exercise in beagle dogs. Zentralblatt Fur Veterinarmedizin Reihe A 44: 449–460. https://doi.org/10.1111/J.1439-0442.1997.tb01130.X

Sutter NB, Bustamante CD, Chase K, Gray MM, Zhao K, Zhu L, Padhukasahasram B, Karlins E, Davis S, Jones PG, Quignon P, Johnson GS, Parker HG, Fretwell N, Mosher DS, Lawler DF, Satyaraj E, Nordborg M, Lark KG and Ostrander EA, 2007. A single IGF1 allele is a major determinant of small size in dogs. Science (New York) 316: 112. https://doi.org/10.1126/science.1137045

Sykes JE, Kittleson MD, Chomel BB, MacDonald KA and Pesavento PA, 2006. Clinicopathologic findings and outcome in dogs with infective endocarditis: 71 cases (1992-2005). Journal of the American Veterinary Medical Association 228: 1735–1747. https://doi.org/10.2460/javma.228.11.1735

Tanweer A, Bano A, Fatima W and Javed H, 2020. Hyperhomocysteinemia: The independent risk factor of cardiovascular diseases. Advancements in Life Sciences 8: 1-7.

Thrusfield MV, Aitken CGG and Darker PGG, 1985. Observations on breed and sex in relation to canine heart valve incompetence. Journal of Small Animal Practice 26: 709–717. https://doi.org/10.1111/J.1748-5827.1985. TB02199.X

Tilley L, Smith F, Oyama M and Sleeper M, 2008. Manual of Canine and Feline Cardiology. Manual of Canine and Feline Cardiology. https://doi.org/10.1016/B978-1-4160-2398-2.x0032-0

Urfer SR, Kaeberlein TL, Mailheau S, Bergman PJ, Creevy KE, Promislow DEL and Kaeberlein M, 2017. Asymptomatic heart valve dysfunction in healthy middle-aged companion dogs and its implications for cardiac aging. GeroScience 39: 43–50. https://doi.org/10.1007/s11357-016-9956-4

Ward J, Mochel JP, Seo YJ and Sathe S, 2020. Effects of the estrous cycle and pregnancy status on cardiovascular variables in healthy bitches. Journal of Veterinary Cardiology 30: 57–68. https://doi.org/10.1016/j.jvc.2020.05.004

Ware WA and Hopper DL, 1999. Cardiac Tumors in Dogs: 1982–1995. Journal of Veterinary Internal Medicine 13: 95–103. https://doi.org/10.1111/j.1939-1676.1999.tb01136.x

Wess G, 2021. Screening for dilated cardiomyopathy in dogs. Journal of Veterinary Cardiology. https://doi.org/10.1016/j.jvc.2021.09.004

Whitney JG, 1974. Observations on the effect of age on the severity of heart valve lesions in the dog. Journal of Small Animal Practice 15: 511–522. https://doi.org/10.1111/J.1748-5827.1974.tb06529.x

Yap KS, Ghanabadi S, Ibrahim Abdul-Azeez Okene AS and Ayarhany S, 2021. Retrospective echocardiographic survey of canine cardiac conditions in Kuala Lumpur, Malaysia. Journal of Animal Health and Production Retrospective 9: 198–204. http://dx.doi.org/10.17582/journal.jahp/2021/9.2.198.204

Youssef G, 2021. Valvular heart diseases in women. Egyptian Heart Journal 73: 1–6. https://doi.org/10.1186/s43044-021-00184-3/metrics