UNIVERSITI PUTRA MALAYSIA

DISTRIBUTION, RISK FACTORS AND SURVIVAL ANALYSIS OF DOG DIAGNOSED WITH DILATED CARDIOMYOPATHY

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DISTRIBUTION, RISK FACTORS AND SURVIVAL ANALYSIS OF DOG DIAGNOSED WITH DILATED CARDIOMYOPATHY

LOW XUEN KANG

A student project paper submitted to the

Faculty of Veterinary Medicine, Universiti Putra Malaysia

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CERTIFICATION

It is hereby certified that I have read this project paper entitled "Distribution, Risk Factors, and Survival Analysis of Dog Diagnosed with Dilated Cardiomyopathy", by Low Xuen Kang and in my opinion it is satisfactory in terms of scope, quality, and presentation as partial fulfillment of the requirement for the course VPD 4999- Final Year Project.

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Specially dedicated to all vets, my family and friends.

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Most importantly, none of this could have happened without my family. Thank you, my parents and siblings, for always being my backbone and giving me all unconditional love. Even though we are apart, family is always in my heart.

CONTENTS

LIST OF ABBREVIATIONS

ACE	Angiotensin-converting enzyme
AUC	Area of curve
CHF	Congestive heart failure
CI	Confidence interval
CLB	Case log book
DCM	Dilated cardiomyopathy
FDA	Food and Drug Administration
GSD	German Shepherd Dog
JDCM	Juvenile dilated cardiomyopathy
kg	Kilogram
MST	Median survival time
No.	Number
OR	Odd ratio
PDK 4	Pyruvate dehydrogenase kinase 4
UVH-UPM	University Veterinary Hospital, Universiti Putra Malaysia
%	Percentage

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ABSTRAK

Abstrak daripada kertas projek yang dikemukakan kepada Fakulti Perubatan Veterinar untuk memenuhi sebahagian daripada keperluan kursus VPD 4999 – Projek.

TABURAN, FAKTOR RISIKO DAN ANALISIS SURVIVAL ANJING YANG DIDIAGNOSI DENGAN KARDIOMYOPATI TERDILAT

Oleh

Low Xuen Kang

2022

Penyelia: Dr Khor Kuan Hua

Penyelia bersama: Dr Norhidayah Noordin

Kardiomiopati terdilat (DCM) adalah jenis kardiomiopati yang paling lazim pada anjing. Kajian ini menentukan taburan, faktor risiko dan kesan pematuhan rawatan terhadap jangka hidup anjing yang didiagnosi dengan DCM. Buku log pesakit anjing di Hospital Veterinar Universiti, University Putra Malaysia, antara 2013 sehingga 2022, dianalisis secara retrospektif, dan jumlah bilangan anjing yang dibentangkan diperolehi. File dari 116 anjing yang didiagnosi dengan DCM disemak secara manual. Maklumat seperti, baka, umur, jantina, tarikh diagnosis dan tarikh meninggal dunia direkodkan untuk kes yang disahkan diagnosis berdasarkan ekokardiografi. Bagi kes dengan maklumat yang tidak lengkap, pemilik dihubungi melalui telefon untuk memastikan status

kesihatan semasa anjing, punca kematian jika pesakit anjing telah meninggal, dan pematuhan pemberian ubat yang ditetapkan. Faktor risiko keminatan dianalisis menggunakan regresi logistik dengan satu dan lebih daripada satu pembolehubah. Median masa survival (MST) diperoleh melalui Kaplan-Meier Estimate. Dalam kajian ini, taburan anjing yang didiagnosis dengan DCM adalah 1.07% (n=116/10846). Anjing jantan (OR: 1.52, 95%CI: 1.00 - 2.32) anjing baka besar (OR: 7.08, 95%CI: 4.17 - 12.03) dan anjing baka sederhana (OR: 2.91, 95%CI: 1.79 -4.72) mempunyai lebih tinggi risko untuk DCM. Sepanjang tempoh kajian, 65 daripada 116 anjing DCM meninggal dunia akibat kematian berkaitan jantung. Pesakit anjing DCM dengan pemilk yang mematuh kepada arahan rawatan mempunyai MST yang lebih lama (549 hari, 95%CI: 392.90 – 705.10) berbanding anjing yang tidak menerima rawatan (148 hari, 95% CI: 35.26 – 260.74). Maklumat diperolehi dapat membenarkan veterinar mencadangkan pemeriksaan serta memotivasikan pemilik untuk menyokong rawatan jangka panjang pada anjing yang terjejas.

Kata kunci: DCM, Kardiomiopati terdilat, taburan, faktor risiko, kebolehan survival

ABSTRACT

An abstract of the project paper presented to the Faculty of Veterinary Medicine as partial requirement on the course VPD 4999 – Final Year Project.

DISTRIBUTION, RISK FACTORS AND SURVIVAL ANALYSIS OF DOG DIAGNOSED WITH DILATED CARDIOMYOPATHY

By

Low Xuen Kang

2022

Supervisor: Dr Khor Kuan Hua

Co- Supervisor: Dr Norhidayah Noordin

Dilated cardiomyopathy (DCM) is the most common type of cardiomyopathy in dogs. This study determined the distribution, risk factors and effect of treatment compliance on the survival of dogs diagnosed with DCM. Log books of canine patients at the University Veterinary Hospital, University Putra Malaysia, between 2013 and 2022, were retrospectively analyzed, and the total number of dogs presented was obtained. Records of 116 dogs diagnosed with DCM were manually reviewed. Information such as breed, age, sex, date of diagnosis and deceased were recorded from cases with a confirmed diagnosis based on echocardiography. For cases with incomplete information, owners were contacted via phone to ascertain the dogs' current health status, cause of death if the dog had deceased, and compliance with the prescribed medications. The risk factors of

interest were analyzed using univariable and multivariable logistic regression. Median survival time (MST) was obtained through Kaplan-Meier Estimate. In this study, the distribution of dogs diagnosed with DCM was 1.07% (n=116/10846). Male dogs (OR: 1.52, 95%CI: 1.00 - 2.32), large breed dogs (OR: 7.08, 95%CI: 4.17 - 12.03) and medium breed dogs (OR: 2.91, 95%CI: 1.79 -4.72) had higher risk for DCM. Throughout the study period, 65 out of 116 DCM dogs succumbed to heart-related death. DCM dogs with compliant owners had significantly longer MST (549 days, 95%CI: 392.90 – 705.10) than those that did not receive treatment (148 days, 95% CI: 35.26 -260.74). Information obtained may allow clinicians to suggest screening and motivate owners to support long-term treatment in affected dogs.

Keyword: DCM; Dilated cardiomyopathy; Distribution; Risk Factors; Survivability

CHAPTER 1.0

INTRODUCTION

1.1 INTRODUCTION

The mortality rate of pet dogs diagnosed with cardiomyopathy is underdiagnosed, perhaps due to a lack of awareness and knowledge among dog owners (Sahoo *et al.*, 2021). Dilated cardiomyopathy (DCM) is an acquired myocardial form of heart disease, and the incident rate was 0.4% among all dogs reported in the United States between 1995 and 2010 (Bellumori *et al.*, 2013). DCM is characterised by chamber dilatation and myocardial systolic and diastolic dysfunction (Tidholm and Jönsson, 2005). Incidence of DCM has been associated with taurine deficiency as early as 1987 and was no longer the main focus until very recently, and the increasing incident was suspected linked to several brands of free grain diet (Adin *et al.*,2019).

DCM is prevalent, particularly in the pure breed dogs, and rarely observed in cross-breed dogs (Dukes-McEwan *et al.*, 2003). Genetic involvement was reported to play a role in contributing to the pathogenesis of DCM. Specifically, autosomal dominant transmission in DCM was reported in Irish Wolfhounds, Newfoundlands, and Dobermanns (Meurs *et al.*, 2007). The prevalence of DCM in pedigree dogs (0.65%) was high compared to crossbreeds (0.16%) and some breeds have shown greater risk, such as the Deerhounds (6.0%), Dobermanns (5.8%), Irish Wolfhounds (5.6%); Great Danes (3.9%); Boxers (3.4%); and Newfoundlands (1.3%) (Dukes-McEwan *et al.*, 2003). Studies revealed that the age and sex of the dogs increased the risk of developing DCM.

The prevalence of dogs diagnosed with DCM increase with age, especially after the age of 7 (Bellumori *et al*., 2013) and was more common in males compared to female dogs (34.0% of all male dogs compared to 19.0% of all female dogs) (Distl *et al.*, 2007)

The treatment of DCM aimed to control the clinical sign, thereby maintaining a good quality of life for as long as possible for the affected dogs. A combination of drugs such as diuretics (furosemide), inodilator (pimobendan) and angiotensin-converting enzyme (ACE) inhibitors are prescribed (Aiello et al., 2016). On the other hand, a study showed that supplementation of taurine and L-carnitine in the diet could partially or completely reverse the DCM that is associated with taurine deficiency (FDA, 2019). Median survival time in dogs diagnosed with DCM treated with digoxin, propranolol and furosemide was reported at 126 days (18 weeks), with a survival rate of 34.0% in the first year after initial diagnosis and 20.0% in the second years (Tidholm, 2006).

1.2 JUSTIFICATION OF THE STUDY

In Malaysia, information on dogs diagnosed with DCM remains lacking. Therefore, this study described the prevalence or occurrences of dogs diagnosed with DCM in the local setting. The risk factor and life expectancy can be concluded from the data collected in a primary healthcare hospital (UVH).

1.3 OBJECTIVES

The objectives of the study were:

1. To determine the distribution of dogs diagnosed with DCM presented in University Veterinary Hospital (UVH) between 2013 to 2022.

2. To investigate the role of age group, breed and sex as risk factors of DCM in dogs.
3. To determine the effect of treatment compliance on the survival time of dogs diagnosed with DCM.

1.3 HYPOTHESIS

The hypothesis for this study were:

1. Ha: Age group, breed, and sex do contribute as risk factors for DCM in dogs.

   H0: Age group, breed, and sex do not contribute as risk factors for DCM in dogs.
2. Ha: DCM dogs with owner compliant with treatment have longer survival time than untreated dogs.

   H0: DCM dogs with owners compliant with treatment have the same survival time than untreated dogs.

CHAPTER 2.0

LITERATURE REVIEW

2.1 Dilated cardiomyopathy in dogs and their prevalence

Dilated cardiomyopathy (DCM) is a primary myocardial disease in dogs. DCM is characterized by enlargement of the left atrium and dilatation of the ventricular, leading to systolic dysfunction (Fuentus *et al*.,2010). Grossly, the affected heart will show the pathological widening of the left ventricle and thinning of the left ventricular wall, which in advanced cases, may affect all heart chambers. Histologically, there are two distinct forms of DCM: fatty infiltration-degenerative type and attenuated wavy fibre type. Attenuated, or in another form, atrophy consists of myocardial cells with a morphology of wavy appearance due to the presence of edematous fluid and fibrosis of the subendocardial layer. On the other hand, the fatty infiltration-degenerative type is characterized by myocytolysis, cardiac fibre degeneration, vacuolization, and atrophy of the myocytes, accompanied by extensive fibrosis and fatty infiltration. This type of DCM was first known as "boxer cardiomyopathy", and is more commonly to be found in mainly Boxer and Doberman Pinschers (Tidholm and Jönsson, 2005).

Bellumori et al. (2013) reported that the prevalence rate of DCM in dogs in the teaching veterinary hospital is 0.4%. Despite DCM being a common cardiomyopathy disease in certain dogs, the aetiology of this disease still remains undetermined.

2.2 Risk factors

Studies that had been made suggested that the development of the disease can be due to multiple factors that result in the myocardia insult, for example, genetics, diets, toxicity, immune-mediated cause, and chronic tachycardia (Fuentus *et al*., 2010). Similar to humans, DCM in dogs has a strong relationship with the genetic constitution with the marked familial transmission. However, the exact interaction between the genetic constitution leading to the expression of the phenotype is still yet come to a conclusion. There were multiple theories on the mechanism of phenotypic manifestation; such as DCM in dogs is a monogenic form of the disease as in humans (Meurs *et al.*,2020), and multiple synergistic mutations in the associated genetic loci and interaction among them causing the development of the disease in the later stage of life (Distl *et al.*, 2007). One example is the Doberman. Doberman is one of the most commonly reported canine breeds diagnosed as DCM patients. In 2012, Meurs *et al.* described that deletion in the pyruvate dehydrogenase kinase 4 (PDK4) gene is identified as associated with the development of DCM in Doberman. PDK4 play a role in regulating cardiac energy metabolism. When PDK4 is affected, glucose oxidation is selected as the primary energy source mechanism rather than high-efficient fatty acid oxidation. A prolonged energy-starve state in the myocardium will lead to degeneration of the myocardium. Another type of DCM which is juvenile dilated cardiomyopathy (JDCM) is commonly diagnosed in Portuguese Water Dog. Through a pedigree analysis, Dambach *et al.* (1999) reported that JDCM in Portuguese Water Dogs follows an autosomal recessive pattern.

In 2019, Food and Drug Administration (FDA) reported that there is a link between certain diets and DCM in dogs. The reported DCM cases between 2014 to 2019 have shown to be possibly associated with grain-free diets that contain non-soy legumes, peas, rice etc. Grain-free diets are associated with various insufficient nutrients, which are directly related to cardiac metabolism. Deficiency in vitamin B6 and B12 that is important for carnitine and taurine synthesis, will lead to DCM. Insufficient intake of amino acid taurine from the commercial diet is also a potential cause of DCM. A taurine-deficient animal will have a myocardium with a lower calcium load, increased troponin I phosphorylation, and decreased excitation-contraction coupling. These changes will lead to decreased myocardial contractility and cause DCM (Ahmad *et al*., 2021)

The infectious agent also plays a role in contributing to the development of DCM in dogs. Viral or bacterial infection-caused myocarditis consequently leads to permanent myocardial damage. Canine parvovirus is one infectious agent that is well-known to cause myocarditis in young puppies. Acute myocarditis will lead to the activation of macrophages and lymphocytes, causing them to release various cytokines and growth factors. Fibroblast is activated by the cytokines to release collagen. Failure of collagen production regulation, continuous collagen deposition in the myocardium and fibrosis due to myocarditis resulted in cardiac remodeling in the left ventricle and, ultimately DCM (Fairweather *et al*., 2011)

Toxicity, immune-mediated causes, and chronic tachycardia are not commonly described, yet suggested as a possible causes of DCM. Doxorubicin is an anthracycline

antitumor medication that is commonly used to treat cancer in dogs. However, the side effects of doxorubicin include arrhythmias and decreased systolic function, which resembles DCM. After 5 doses of doxorubicin administration, clinical cardiotoxicity is found with decreased fractional shortening and development of ventricular premature contractions (Hallman *et al.*, 2019). Autoimmunity and chronic tachycardia have also shown to be related to the development of DCM in dogs; however, the occurrences in dogs is lacking.

2.3 Treatment

According to Fuentus *et al.* (2010), treatment of DCM is merely palliative. The goal of treatment in DCM dogs is to i) relieve the clinical sign, ii) improve the quality of life, and iii) increase survivability. The median survival time of DCM without treatment is 65 days, with a probability of DCM dogs getting through the first year being 37.5% (Monnet *et al.*, 1999). Without treatment, DCM dogs will experience poor quality of life due to cardiac cachexia. After a long period, the dogs will succumb to congestive heart failure or even sudden death before the progression of the disease in certain breeds of dogs. Management of DCM is mainly through medication and dietary management. Medication is given mainly to i) improve the contractility of the heart, ii) blunt the neurohormonal activation of angiotensin II, iii) remove the excess fluid in the body cavity, iv) improve the blood pressure, and v) treat arrhythmias (Tilley *et al.*,2008). Diuretics, ACE inhibitors, vasodilators, positive inotropic drug, calcium channel blockers, and beta blocker is distributed to DCM patients depending on the severity of the clinical sign to

relieve the symptoms. For dietary management, salt restriction is a necessity to avoid excess sodium consumption that can raise blood pressure and accelerate the development of congestive heart failure. Supplementation of specific nutrient such as taurine and also L-carnitine is also crucial for DCM dogs.

CHAPTER 3.0

MATERIALS AND METHODS

3.1 SOURCE OF DATA

The retrospective study of canine dilated cardiomyopathy (DCM) was conducted at the University Veterinary Hospital of University Putra Malaysia (UVH-UPM). The case file number of canine diagnosed with DCM between year 2013 to 2022 were retrieved manually from the Case Log Book (CLB) in the UVH. The total number of canine patients visited UVH over the course of ten years were calculated and the number of DCM patient was filtered out and recorded. All the patient medical records diagnosed with DCM and those of suspected DCM were manually retrieved. Information such as case number, name, breed, body weight, age and sex were recorded. All the individual case files were reviewed to reconfirm that cases included were diagnosed as DCM.

3.2 INCLUSION CRITERIA

The inclusion criteria for this study including those dog patient that diagnosed with DCM with i) retrievable case file in UVH, ii) complete patient signalment, iii) complete information on clinical sign and physical examination findings associated to the DCM and iv) confirmed diagnosis of canine DCM based on echocardiograph. Complete patient signalment must include age, breed, sex, body weight, date of diagnosis, date of deceased if passed away and medication prescribed.

3.3 RISK FACTORS ANALYSIS FOR AGE, BREED AND SEX

The age of the dogs was recorded and re-group into puppy, adult and senior dogs based on a guide from the WALTHAM® Pocket Book of Human-Animal Interactions (2017). Puppy group were defined as dogs of less than one-year-old, adult dog group were between 1.0 to 6.9 years old, and senior dog group were 7 years old and above. The dogs classified according to their breed size into small, medium and large breed based on the American Kennel Club standard. As for local breed and mixed breed, their body weight will be used as a reference for breed size. Small breed dogs weigh from 1.0kg to 9.9kg, medium breed dogs weigh from 10.0kg to 19.9kg, and large breed dogs were those weighing 20kg and above. The sex of the dogs was recorded as either male or female.

3.4 DEFINITIVE DIAGNOSIS

In order to confirm the diagnosis of DCM, information consist of history, clinical sign, physical examination, and findings from radiography and echocardiography must be available. Each file was examined thoroughly with the clinician prior to recruitment in the study.

3.5 EXCLUSION CRITERIA

Cases with non-definitive diagnosis, such as suspected DCM cases with incomplete evidence for diagnosis, whether there was no evidence of affirmative radiographic, echocardiographic result was excluded from the analysis. Case files that were failed to retrieve or incomplete patient signalment were also excluded from the study.

3.6 TREATMENT AND SURVIVAL DAYS

The current health status (either dead or alive) of each DCM dogs was obtained from the case file or if unknown, their respective owner was contacted through a phone call to obtain further information. The date of diagnosed is based on the date when the dog was diagnosed with DCM (based on the echocardiogram) as stated in the case file. The endpoint of each individual patient study was either the date of deceased (dead) or if still alive, the cut-off date was set on 31st of August 2022. Deceased dogs due to complication of DCM or euthanized due to progressive heart failure were counted as deaths related to DCM and those were still alive at the end of the study period were used for survival analysis. Deceased dogs with cause of deaths unrelated to DCM were censored in the analysis.

3.7 STATISTICAL ANALYSIS

All data were tabulated in Microsoft Excel (2016) and statistical analysis was performed using SPSS (IBM, USA). The proportion of DCM patients and cardiac disease patient was calculated by dividing the confirmed cases with the total number of dog case presented in UVH over the period of ten years. The risk factors (age, breed size and sex) towards DCM were investigated using univariate and multivariate logistic regression. The senior age group, small breed size, and female were used as reference. All factors possessing $p<0.05$ after univariate logistic regression were submitted as considerable risk factors for multivariate logistic regression to investigate how the factors interacts with each other. Kaplan-Meier Estimator test was performed to determine the survivability of

DCM dogs with or without treatment. The median survival time was obtained in days when the deceased population reached 50% of the total DCM patients. The treatment was shown to have significant association to survivability in DCM patient when the log rank test was $p<0.05$.

CHAPTER 4.0

RESULTS

4.1 DISTRIBUTION OF CANINE PATIENT IN UVH-UPM

In this study, 10846 canine cases were presented to UVH-UPM between 2013 to 2022. Out of 10846 cases, the total number of cardiac disease patients was 1129 (10.4%). Out of the 1129 cardiac disease patients, 116 of the dogs with diagnosed with DCM. Therefore, the distribution of dog diagnosed with DCM was 10.3% among the cardiac disease dogs and 1.1% in this study population (Refer Figure 1).

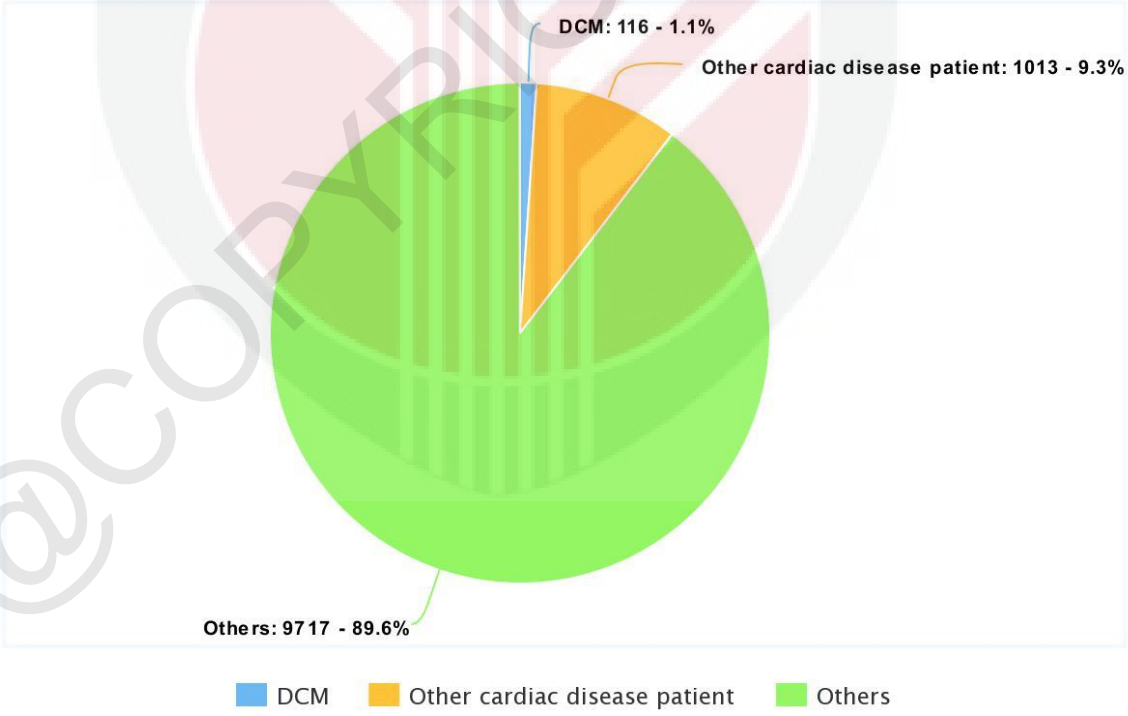

Figure 1: Distribution of canine patient in UVH-UPM from 2013-2022

4.1.1 Distribution of age, breed and sex for DCM patients

Out of the 116 DCM dogs, majority of them were senior age group (70.1%, n=82) (refer Figure 2), medium breed size (41.0%, n=48) (refer Figure 3) and male (65.8%, n=77) (refer Figure 4) dogs. The three major breeds of dogs commonly presented with DCM were local breed (n=20), Labrador (n=16) and Shih Tzu (n=13), with other breeds of dogs listing in Table 1.

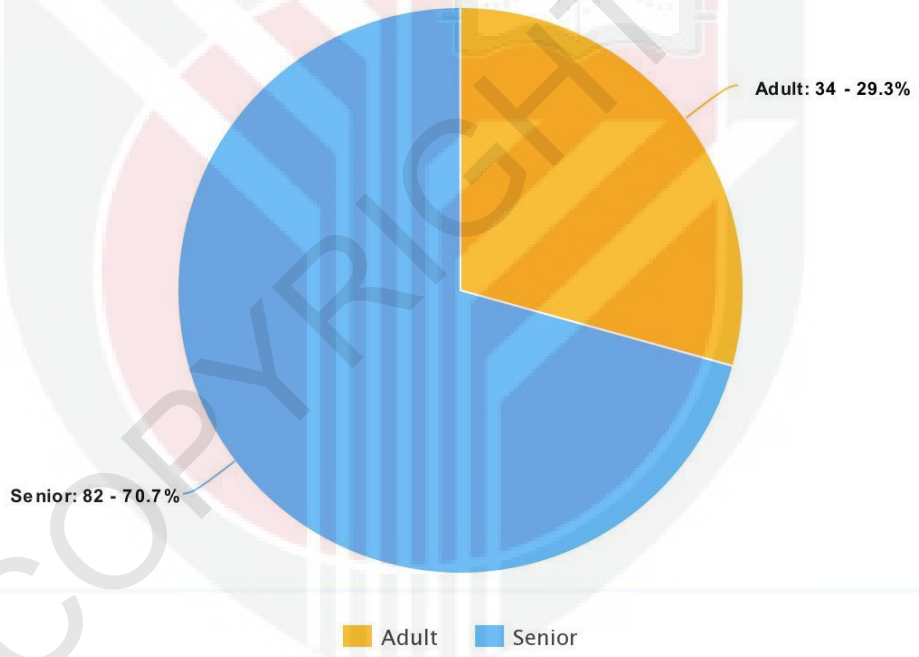

Figure 2: Age group for canine patients diagnosed as DCM in UVH-UPM.

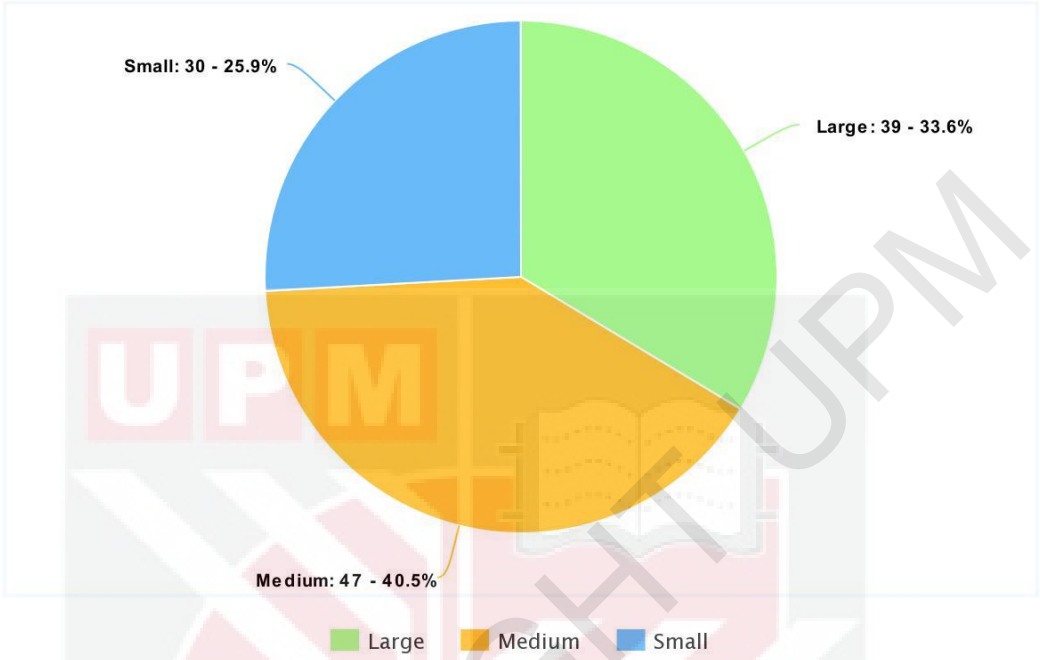

Figure 3: Breed size for canine patient diagnosed as DCM in UVH-UPM.

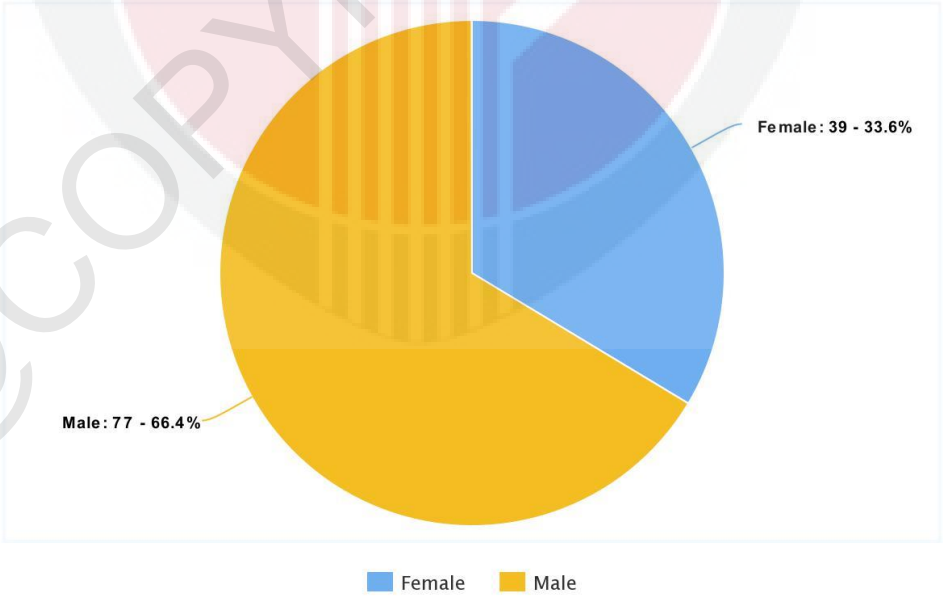

Figure 4: Sex of the canine patient diagnosed as DCM in UVH-UPM.

Table 1: Breed distribution of dogs diagnosed with DCM in UVH-UPM from September 2013 to August 2022.

Breed	Number (n)	Percentage (%)
Local	20	17.2
Labrador	16	13.8
Shih Tzu	12	10.3
Cocker Spaniel	8	6.8
Dobermann	6	5.2
Golden Retriever	6	5.2
Beagle	4	3.4
GSD	4	3.4
Pomeranian	4	3.4
Dalmatian	3	2.6
Spitz	3	2.6
Terrier	3	2.6
Mixed	3	2.6
Bull Terrier	2	1.7
English Springer Spaniel	2	1.7
Miniature Pinscher	2	1.7
Miniature Schnauzer	2	1.7
Poodle	2	1.7

Rottweiler	2	1.7
Silky Terrier	2	1.7
American Cocker Spaniel	1	0.9
Border Collie	1	0.9
Boxer	1	0.9
Bulldog	1	0.9
Chow Chow	1	0.9
French Bulldog	1	0.9
Malinois	1	0.9
Maltese	1	0.9
Pug	1	0.9
Schnauzer	1	0.9
Total	116	100.0

4.2 Risk factors

The univariate logistic regression showed that age, breed, and sex were statistically significant risk factors for DCM ($p<0.05$) (Table 2). In terms of breed size, large breed dogs were at greater risk of being diagnosed with DCM (Odds ratio, OR=7.37, 95% CI: 4.35-12.47).

All risk factors were then submitted for multivariable logistic regression. Hosmer-Lemeshow were not significant at $p>0.05$, indicating a good fit, with the area of

curve (AUC) of 0.71. The multivariate logistic regression model was statistically significant ($\chi 2 = 11.46$, $p < 0.05$) and correctly classified 88.2% of the case. There was a significant association between breed size and sex in dogs with DCM (Table 3). Male dog and larger breed size had a higher risk of developing DCM than other dogs ($p<0.05$). In contrast, age group was not a significant risk factor for DCM after adjusting with gender and breed size.

Table 2: Univariate logistic regression analyses between risk factors (sex, age group, and breed size) and DCM in 116 dogs presented to the University Veterinary Hospital, Universiti Putra Malaysia (UVH-UPM) between September 2013 and August 2022.

Factors	**X^2**	**P value**	**β**	**Crude OR (95% CI)**	**P Value**
Age Group	4.38	0.04			
Senior			-	Ref	-
Adult			0.49	1.64 (1.07-2.51)	0.02*
Breed size	58.51	<0.001			
Small			-	Ref	-
Medium			1.08	2.96 (1.82-4.80)	<0.001*
Large			2.00	7.37 (4.35-12.47)	<0.001

Sex	4.94	0.03			
Female			-	Ref	-
Male			0.45	1.57 (1.05-2.35)	0.03*

X^2=Pearson chi-square; **β**=unstandardized regression coefficient; OR: odds ratio; CI: confidence interval; Ref: reference; *P<0.05

Table 3: Multivariate logistic regression analyses between risk factors (sex, age group, and breed size) and DCM in 116 dogs presented to the University Veterinary Hospital, Universiti Putra Malaysia (UVH-UPM) between September 2013 and August 2022.

Factors	**X^2**	**P value**	***β***	**Adjusted OR (95% CI)**	**P value**
Age Group	4.38	0.04			
Senior			-	-	-
Adult			0.32	1.38 (0.88-2.16)	0.16
Breed size	58.51	<0.001			
Small			-	-	-
Medium			1.07	2.91 (1.79-4.72)	<0.001*
Large			1.96	7.08 (4.17-12.03)	<0.001*

Sex	4.94	0.03			
Female			-	-	-
Male			0.42	1.52 (1.00-2.32)	0.048*

X^2=Pearson chi-square; **β**=unstandardized regression coefficient; OR: odds ratio; CI: confidence interval; *P<0.05

4.3 Survival analysis

Out of the one hundred and sixteen DCM dogs, sixty-five dogs had DCM related death and eight dogs had non-DCM related death. Twenty-three dogs were still alive until 31st August 2022 and twenty DCM dogs were lost to follow-up after 10 years. The median survival time for DCM dogs with owner compliant to the treatment showed significant survival time ($p<0.05$) compared to DCM dogs without treatment, with survival time of 549 days (95% CI: 392.9 -705.1) versus 148 days (95%CI: 35.3 - 260.7) respectively (Figure 5 and Table 4).

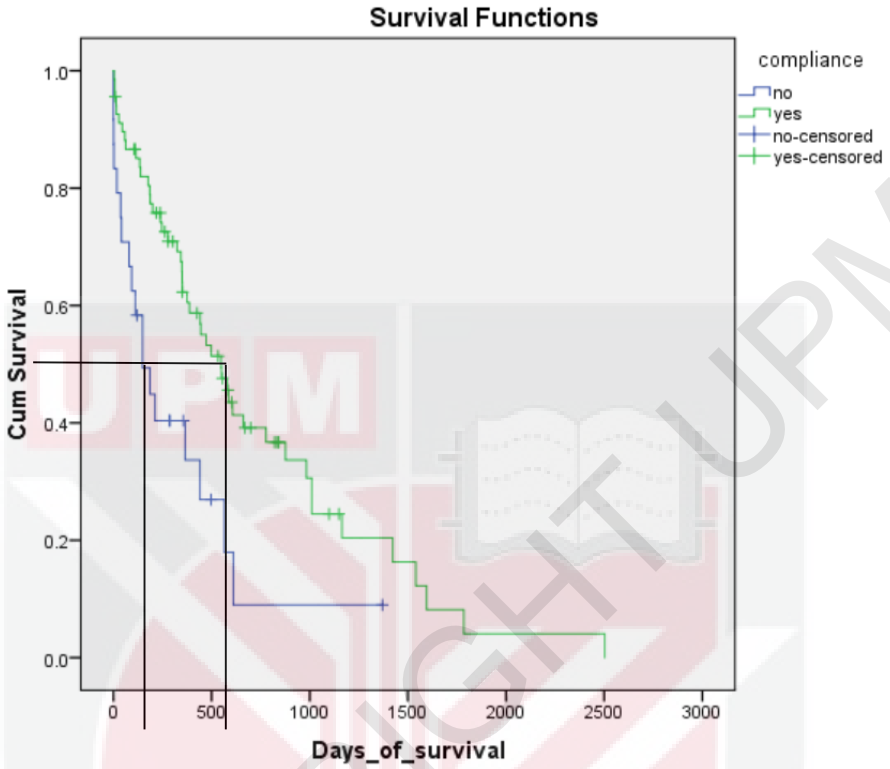

Figure 5: Kaplan-Meier Plot for the survival analysis of DCM dogs with or without owner compliant to the treatment in UVH-UPM.

Table 4: Kaplan-Meier analysis of median survival time of DCM dogs with or without owner compliant to the treatment in UVH-UPM.

	Median			
	Estimate	Standard Error	95% Confidence Interval	
Compliance			Lower Bound	Upper Bound
Non-compliant	148.00	57.52	35.26	260.74

Compliant	549.00	79.64	392.90	705.10
Overall	442.00	89.68	266.22	617.78

CHAPTER 5.0

DISCUSSION

This study provides information on the distribution, risk factors, and survival analysis of DCM dogs presented to a teaching hospital (UVH-UPM). The distribution of canine cardiac disease patients in UVH-UPM was at 10.4% (n=1129/10846), while the distribution of DCM patients was at 1.1% (n=116/10846). By comparing with the DCM prevalence rate reported in a veterinary teaching hospital by Bellumori *et al.* (2013), which is at 0.4%, the distribution rate has increased. There is a possibility in a rising trend of DCM among the dogs in Malaysia, perhaps related to increased exposure of risk factors such as diet (McCauley *et al.*, 2020) or the growing trend of adopting pure-breed dogs as pets (Ho *et al.*, 2021). As the COVID-19 pandemic struck during the past 3 years, the number of pet have risen significantly (Grejfoner *et al.*, 2021) due to various reasons such as companionship, emotional support and a sense of security.

In this study, breed and sex played significant risk factor for dogs towards being diagnosed with DCM. The large breed size dogs were shown to be at higher risk of diagnosed with DCM. DCM was often related with genetic basis, and genetic mutation has been reported as predisposing factor in certain medium and large breed dogs for example Doberman Pinscher and Boxer. Meurs *et al.* (2012) reported that deletion of PDK4 gene identified in Doberman Pinscher was found to be associated with the development of familial DCM. Another study made by Meurs et al (2013) demonstrated

that the presence of striatin gene mutation contributed strong positive association with the development of DCM in Boxer dogs.

Studies have reported that male dogs were likely more affected than the female dogs with DCM (Distl *et al.*, 2007; Tilley *et al.*, 2008). Similar was observed in this study where the male dogs were 1.52 times more likely to be diagnosed as DCM patients compared to female dogs. This conclusion often relates to the mode of inheritance of the DCM condition. Several modes of inheritance of DCM have been suggested in the past, including autosomal monogenic dominant mode of inheritance (Dukes-McEwan and Jackson, 2002), autosomal monogenic recessive mode of inheritance (Dambach *et al.*, 1999), X-linked recessive mode of inheritance (Distl *et al.*, 2007). An X-linked recessive mode of inheritance is the type of inheritance that lead to the increased occurrence in male, as reported in Great Dane (Meurs *et al.*, 2001) and Doberman Pinscher (Simpson *et al.*, 2015). An X-linked susceptible DCM male can either possesses XY alleles or xY alleles, while a susceptible DCM female can possess XX, Xx, or xx alleles. Females will have a lower incidence than males as only the homozygous xx alleles will lead to the development of DCM in the later stage of life (Simpson *et al.*, 2015).

Tilley *et al.* (2018) reported that the typical age of diagnosis is at 6-8 years, indicating that DCM often develops in the later stage of life in dogs. Inoue *et al.* (2016) also reported that the odds of diagnosed as DCM patients is increased by 1.5 times as their age increased by one year. However, age was not a significant risk factor in this study. The onset of clinical signs presented by the dogs is heterogeneous and varies between

different ages and breeds. Gaar-Humphrey *et al.* reported that the onset of DCM in Irish Wolfhounds was at 4.4 years, while Great Dane was at 4.8 years. However, the mean age of onset for Dobermans can be up to 8.6 years old. DCM dog first clinical presentation is also heavily depending on the owner's awareness of their dogs and knowledge of the clinical signs of heart disease. Early clinical signs for DCM can be very subtle and neglected by the owner, therefore delaying their first clinical diagnosis.

DCM dogs often requires lifelong medication to prevent the progression of the disease and maintain a good quality of life, especially at the later stage of DCM. Thus, the treatment regime is very important as it affects the survivability of the patients. In this study, the median survival times increased by 3.7 times when a DCM patient received the correct treatment in companion with a compliant owner. This finding is consistent with a study made by Fuentus *et al.* (2008), in which he stated that Doberman with DCM treated with pimobendan had a longer survival time of 329 days compared to the placebo class with survival times of 50 days. Keene *et al.* (1991) also stated that compliant owners that able to provide their DCM dogs with a balanced, nutritious diet with carnitine supplement also shown to help in restoring the myocardial function in myocardial carnitine deficient-associated DCM, consequently improving the survivability in DCM dogs.

CHAPTER 6.0

CONCLUSION

The prevalence of DCM in UVH-UPM from 2014 to 2018 was 1.1% (n=116/10846). The male, large and medium breed dogs were at a higher risk of developing DCM. This study provides veterinarians information on the occurrences and risk factors of dogs towards DCM, and thus may increase the awareness of both veterinarians and owners on early signs of DCM. Early heart screening was suggested as early as 12 months old and annually to promote early detection of the disease. Early intervention of disease by medication may aid in reversing the condition in cases of myocardial carnitine deficient-associated DCM or at least delaying the onset of congestive heart failure (CHF) that affects the quality of life of affected dogs. Compliance from the owner is also very crucial in terms of following the veterinarian's advice and keeping up with medication to prolong the survival of dogs.

CHAPTER 7.0

RECOMMENDATION

For recommendation, UVH can implement routine practice in enquiring dog's management in term of type of diets, different ingredients used for feeding and dietary supplementation of dogs and especially those with heart disease to allow a better risk factors investigation. Measurement of serum taurine level of DCM dogs can be done along with taurine analysis in their daily diet for the investigation of taurine-deficient DCM. Last but not least, development and innovation guideline of genetic testing in UVH may allow promotion of early screening among dogs at risk and may provide more insight on DCM in dogs.

CHAPTER 8.0

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