UNIVERSITI PUTRA MALAYSIA

QUALITY OF LIFE ASSESSMENT OF DOGS DIAGNOSED WITH DEGENERATIVE MITRAL VALVE DISEASE BEFORE AND AFTER TREATMENT

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CERTIFICATION

It is hereby certified that we have read this project paper entitled "Quality of Life Assessment of Dogs diagnosed with Degenerative Mitral Valve Disease Before and After Treatment" by Chee Yuet Yien and in our opinion, it is satisfactory in terms of scope, quality and presentation as partial fulfilment of the requirement for the course VPD 4999-Project.

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Specially dedicated to all vets, my family and friends.

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LIST OF ABBREVATIONS

AAHA	: American Animal Hospital Association
ACE-i	: Angiotensin Converting Enzyme inhibitor
AUC	: Area under the curve
CHF	: Congestive heart failure
CKCS	: Cavalier King Charles Spaniel
DMVD	: Degenerative Mitral Valve Disease
FPV	: Faculty of Veterinary Medicine
LVIDd	: Left ventricular internal diameter during diastole
N.T.- proBNP	: N-terminal fragment B-type natriuretic peptide
PCV	: Packed cell volume
QoL	: Quality of life
RAAS	: Renin-angiotensin-aldosterone system
SPSS	: Statistical Package for the Social Sciences
UVH	: University Veterinary Hospital
UVH-UPM	: University Veterinary Hospital, Universiti Putra Malaysia
VHS	: Vertebral heart score
VLAS	: Vertebral left atrial size

ABSTRAK

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

PENILIAIAN KUALITI KEHIDUPAN ANJING DIDIAGNOSIS DENGAN PENYAKIT INJAP DEGENERATIF SEBELUM DAN SELEPAS RAWATAN

Oleh

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Penyakit injap mitral degeneratif (DMVD) merupakan penyakit jantung paling prevalens dalam kalangan anjing. Pengurusan jangka panjang anjing dengan DMVD bertujuan untuk meningkatkan kualiti kehidupan (QoL). Justeru, penilaian QoL amat penting untuk merangka strategi rawatan yang bermanfaat kepada pesakit. Kajian ini bertujuan untuk menentukan i) bahawa rawatan dapat menambahbaikkan QoL dan penemuan radiografi, ii) pilihan rawatan yang efektif bagi anjing pada Peringkat C dan D, serta iii) korelasi antara QoL dan penemuan radiografi. Kajian retrospektif 10 tahun ini melibatkan sebanyak 149 kes fail anjing-klien di Hospital Veterinar Universiti, Universiti Putra Malaysia (UVH-UPM) yang menghidapi DMVD Peringkat C dan D. Maklumat QoL yang diambil adalah terdiri daripada kebajikan (berat badan, selera, kelesuan, intoleransi senaman), pemboleh ubah pernafasan (sesak nafas, batuk, mengah, pernafasan abdomen), pemboleh ubah peredaran darah (sianosis, pitam), skor jantung vertebra

(VHS) dan saiz atrium kiri vertebra (VLAS). Perbandingan dibuat antara rawatan menggunakan inodilator dan perencat enzim pengubah angiotensin (ACE-i). Data yang dikumpul dianalisis dengan statistik deskriptif, ujian Friedman, ujian Mann-Whitney U, ujian Kruskal-Wallis H dan analisis korelasi Spearman. Pemboleh ubah QoL (selera, kelesuan, intoleransi senaman, sesak nafas, batuk, mengah, pernafasan abdomen serta pitam) menunjuk penambahbaikan yang signifikan selepas rawatan (hari 60 dan 180) ($p<0.05$). ACE-i meningkatkan berat badan dan mengurangkan sianosis ($p<0.05$) dengan signifikan pada Peringkat D, serta VHS ($p=0.03$) pada Peringkat C. Peningkatan VLAS dikaitkan secara positif dengan pernafasan abdomen ($p=0.02$) dan pitam ($p=0.02$). Oleh itu, VLAS boleh berfungsi sebagai penunjuk prognostik bagi pernafasan abdomen dan pitam. Kajian ini menyimpulkan bahawa rawatan meningkatkan QoL di antara anjing DMVD Peringkat C atau Peringkat D. Namun, tiada perbezaan dari segi QoL antara anjing Peringkat C yang berlainan kumpulan rawatan, manakala anjing peringkat D yang dirawat menggunakan ACE-i menunjukkan penambahbaikan berat badan dan pengurangan sianosis. Anjing Peringkat C yang dirawati dengan ACE-i mempunyai saiz jantung yang lebih kecil.

Kata Kunci: penyakit injap mitral degeneratif, kualiti kehidupan, rawatan, skor jantung vertebra, saiz atrium kiri vertebra

ABSTRACT

An abstract of the project paper presented to the Faculty of Veterinary Medicine in partial fulfilment of the course VPD 4999- Project.

QUALITY OF LIFE ASSESSMENT OF DOGS DIAGNOSED WITH DEGENERATIVE MITRAL VALVE DISEASE BEFORE AND AFTER TREATMENT

by

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2023

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Canine degenerative mitral valve disease (DMVD) is dogs' most prevalent heart disease. Long-term management of dogs with DMVD aims to improve the quality of life (QoL). Hence, QoL assessment is essential for formulating treatment strategies that benefit patients. This study aimed to determine i) that treatment improved QoL and radiographical findings, ii) the effective treatment regime for each Stage C and D dog, and iii) the correlation between QoL and radiographic characteristics. A 10-year retrospective study was conducted at the University Veterinary Hospital, Universiti Putra Malaysia (UVH-UPM), and case files of 149 client-owned dogs with DMVD in Stages C and D were retrieved. Information for QoL such as well-being (body weight, appetite, lethargy, exercise intolerance), respiratory variables (dyspnoea, coughing, panting, abdominal breathing), circulatory variables (cyanosis, syncope), vertebral heart score

(VHS) and vertebral left atrial size (VLAS) was recorded. Comparison was made between treatments using inodilators and angiotensin-converting enzyme inhibitors (ACE-i). The collected data were subjected to descriptive statistics, Friedman's test, Mann-Whitney U test, Kruskal-Wallis H test and Spearman's correlation analysis. QoL variables (appetite, lethargy, exercise intolerance, dyspnoea, coughing, panting, abdominal breathing and syncope) showed significant improvement after treatment (day-60 and -180) ($p<0.05$). ACE-i significantly ($p<0.05$) improved body weight and cyanosis in Stage D, and VHS ($p=0.03$) in Stage C dogs. An increase in VLAS was positively correlated with abdominal breathing ($p=0.02$) and syncope ($p=0.02$). Therefore, VLAS may be used as a prognostic indicator for abdominal breathing and syncope. This study showed that treatment improves the QoL of dogs with Stage C or Stage D DMVD. There was no difference in QoL between treatment groups of Stage C dogs but, Stage D dogs treated with ACE-i had better improvement in body weight and cyanosis. Stage C dogs treated with ACE-i had smaller heart sizes.

Keywords: degenerative mitral valve disease, quality of life, treatment, vertebral heart score, vertebral left atrial size

1.0 Introduction

Degenerative mitral valve disease (DMVD) is the most commonly presented cardiac disease among small-breed geriatric dogs above 13 years old (Keene *et al.*, 2019). DMVD is described as the progressive degeneration of the mitral valves, eventually causing heart failure (Häggström *et al.*, 2004; Borgarelli and Häggström, 2010). The American College of Veterinary Internal Medicine (ACVIM) has classified DMVD into five stages to ease justifications for diagnosis and treatment (Keene *et al.*, 2019).

Clinical signs vary according to stages of DMVD, with the onset of clinical signs occurring in dogs with DMVD Stage C. Left-sided heart failure clinical signs due to DMVD comprises of tachypnoea, dyspnoea, lethargy and cough. The negative impact of heart disease on human QoL can be related to dogs using congestive heart failure (CHF) clinical signs such as dyspnoea, exercise intolerance and lethargy (Juenger *et al.*, 2002; Freeman *et al.*, 2005).

Nevertheless, upon generic assessments, the QoL of young healthy animals is not necessarily better than old or diseased animals since QoL is a multifactorial variable. Thus, disease-specific assessment tools are more helpful in evaluating health-related QoL (Fulmer *et al.*, 2022).

Current pharmacological treatments focus on mitigating damages due to mitral insufficiency (Häggström *et al.*, 2004). Medical therapy was proven to lengthen time towards the primary endpoint in studies such as Quality of Life and Extension of Survival Time (QUEST) and Benazepril in Canine Heart disease (BENCH), delaying cardiac-related deaths, euthanasia or treatment failures [BENCH (BENazepril in Canine Heart disease) Study Group, 1999; Häggström *et al.*, 2008].

With pet owners reluctant to see their pets experience what they perceive as suffering, it is essential to determine whether a prolonged lifespan with medical treatments benefits the patients. This can be done using QoL assessment tools (Freeman *et al*., 2005; Oyama *et al*., 2008; Fulmer *et al.*, 2022). QoL assessment tools can be used to make decisions that are in the best interest of patients (Freeman *et al.*, 2005; Fulmer *et al.*, 2022).

1.1 Justification, objectives and hypothesis

1.1.1 Justification of the study

DMVD is the most common cardiac disease in small breed, senior dogs, and its survival time can be prolonged with therapy. Therefore, it is essential to determine if the extended survival time via treatments is in the patient's best interests by utilising QoL assessment.

QoL studies often employ a prospective approach that relies on structured tools such as the Functional Evaluation of Cardiac Health (FETCH) Questionnaire for Dogs to evaluate owner reports of patient QoL. It allows the veterinarian to obtain in-depth and accurate information regarding the owner's concerns, which might otherwise be missed during consultation. The practice of QoL assessment has never been conducted locally.

1.1.2 Objectives of the study

The objectives of this retrospective study were:

1) To determine the scores of QoL in dogs affected by DMVD before and after treatment.
2) To compare the efficacy of different treatment plans in improving the QoL in dogs affected by DMVD.

1.1.3 Hypothesis of the study

1) $H_{0:}$ There is no difference in QoL of DMVD dogs before (day-0) and after (day-60, day-180) treatment.

   $H_{.A.}$: There is a difference in QoL of DMVD dogs before (day-0) and after (day-60, day-180) treatment.

2) $H_{0:}$ There are no differences in QoL assessment scores of DMVD dogs treated with angiotensin-converting enzyme inhibitors (ACE-i), inodilators or both.

   $H_{.A.}$: There are differences in QoL assessment scores of DMVD dogs treated with angiotensin-converting enzyme inhibitors (ACE-i), inodilators or both.

3) $H_{0:}$ There is no correlation between vertebral heart score (VHS) and vertebral left atrial size (VLAS) with clinical signs displayed.

   $H_{.A.}$: There is a correlation between vertebral heart score (VHS) and vertebral left atrial size (VLAS) with clinical signs displayed.

2.0 Literature review

2.1 Degenerative mitral valve disease

DMVD refers to the progressive degeneration of the mitral valve, eventually causing left-sided CHF (Häggström *et al.*, 2004; Borgarelli and Häggström, 2010). It has been coined under terms such as myxomatous mitral valve disease, chronic valvular disease, endocardiosis, and mucoid degeneration (Borgarelli and Buchanan, 2012; Abbott, 2015).

DMVD remains the most prevalent heart disease, responsible for 75.00% of cardiac conditions presented in North America (Keene *et al.*, 2019). In Malaysia, among heart diseases presented to the University Veterinary Hospital, Universiti Putra Malaysia (UVH-UPM), mitral valve diseases accounted for 67.90% of the cases diagnosed (Noordin *et al.*, 2022). Another study revealed that DMVD cases comprised 66.30% and 64.20% of cardiac diseases in dogs presented in 2016 and 2017, respectively (Sin *et al.*, 2021).

Complications of DMVD generally include mitral valve insufficiency, prolapse, and lesions that spread and involve surrounding structures causing rupture and tears (Fox, 2012).

2.2 Anatomy of the mitral valve and pathological changes

The mitral valve comprises leaflets, mitral valve annulus, chordae tendineae, papillary muscles, and surrounding cardiac walls. The integration of these components contributes to maintaining its functionality in preventing the mixing of inflow and outflow blood (Fox, 2012).

Several structures of the mitral valve assist in minimising wear and tear as the leaflets' curvature is adapted to mitigate stress (Fox, 2012). The mitral valve annulus the ensures vertical direction of the systolic forces upon the mitral valve leaflets, preventing mitral regurgitation (Grewal *et al.*, 2010; Borgarelli *et al.*, 2011). Alterations cause further complications, eventually resulting in a vicious cycle in which the heart tries to compensate by undergoing more abnormal changes (Fox, 2012).

Gross changes are localised to the mitral valve leaflets and chordae tendineae. Leaflets thicken and protrude into the atrium upon coaptation (Häggström *et al*., 2004; Han *et al.*, 2010). Nodules and bulges often on distal segments of the leaflets can coalesce and extend towards the chordae tendineae with disease progression (Häggström *et al*., 2004; Borgarelli and Buchanan, 2012). Lengthening and rupture of chordae tendineae occur as DMVD exacerbates (Markby *et al.*, 2017).

Whitney *et al.* differentiate valve changes into four types, emphasising nodular formation, chordae tendineae condition, and valve functionality (Whitney, 1967).

Histologically, a typical mitral valve apparatus comprises four layers: atrialis, fibrosa, spongiosa, and ventricularis layers (Fox, 2012). The previous name, 'myxomatous', illustrates the histological changes of spongiosa layer proliferation and fibrosa layer decrease commonly found in affected dogs (Borgarelli *et al.*, 2011; Ljungvall and Häggström, 2017). Myxomatous degeneration causes changes in connective tissue components of the valve and chordae tendineae, leading to abnormalities in arrangement, proteoglycan content, and collagen deposition. Elevation of mast cells and macrophages can be found primarily in the distal sections

of valve leaflets, but the role of these mononuclear cells has yet to be confirmed (Han *et al.*, 2008; Markby *et al.*, 2017).

Interstitial cells remain spindle-shaped, transforming phenotypically to (a-SMA)-positive cells that are suspected to be associated with disease development. Stromal cells experience genetic change, while endothelial cells suffer from cellular pleomorphism and damage due to jet lesions (Fox, 2012; Markby *et al.*, 2017).

2.3 DMVD epidemiology and natural history

The prevalence and severity of DMVD heavily revolve around breed, gender, and age. Depending on the method of diagnosis, DMVD generally displays a high prevalence among geriatric, small-breed dogs above ten years of age.

DMVD appears to be a polygenic defect, contributed by the interaction of multiple genes leading to valvular disease (Häggström *et al.*, 1995; Olsen *et al.*, 1999; Lewis *et al.*, 2011). The genes responsible for the small size of certain dog breeds [Cavalier King Charles Spaniel (CKCS), Dachshunds] are also involved in the valvular formation, such as IGF1 and SMAD2, potentially causing predisposition among younger dogs. However, the correlation between these genes and DMVD has yet to be demonstrated (Borgarelli and Häggström, 2010; Parker and Kilroy-Glynn, 2012).

Male dogs develop the disease earlier and faster than female dogs (Olsen *et al.*, 1999; Häggström *et al.*, 2004; Lundin and Kvart, 2010). Affected male dogs display more severe clinical signs such as mitral valve prolapse, mitral regurgitation and heart murmurs (Lundin and Kvart, 2010; Lewis *et al.*, 2011). Nevertheless, the influence of gender on DMVD prevalence remains debatable, but the earlier appearance of

symptoms and greater severity may cause a difference in gender categories presented for DMVD (Lundin and Kvart, 2010; Borgarelli and Buchanan, 2012).

In addition, DMVD severity progresses with age as stresses on the mitral valve increase, causing further thickening of the mitral valve leaflets and mitral regurgitation. Mitral valve leaflets are subjected to constant stress from haemodynamic and systolic forces. Over time, the unequal distribution of stresses and annular dilation results in myxomatous degeneration, causing further compromise of valvular function and a vicious cycle of degeneration (Olsen *et al.*, 1999; Borgarelli and Häggström, 2010; Fox, 2012; Borgarelli *et al.*, 2011; Borgarelli and Buchanan, 2012; Keene *et al.*, 2019).

Morphological factors were speculated to play a role in DMVD prevalence, based on previous research on humans and other animal species. A shorter height and smaller thoracic cavity correlate to increased cardiovascular disease risk in humans. With the heart shrinking slower than the thoracic cavity, overcrowding and valvular abnormalities occur (Häggström *et al.*, 2004; Parker and Kilroy-Glynn, 2012). This is apparent in Dachshunds, whose narrow chest is linked to a higher risk of mitral valve prolapse (Häggström *et al.*, 2004).

2.4 American College of Internal Veterinary Medicine DMVD staging

DMVD is classified into four stages based on a staging system developed by the ACVIM, published in 2019, considering breed risk factors, morphological changes and clinical signs to facilitate diagnosis and treatment.

Table 1: ACVIM DMVD Staging in Dogs		
Stage	Definition	Further recommendations
Stage A	Dogs with a genetic predisposition to DMVD such as CKCS, Dachshunds and Toy Poodles with healthy cardiological functions.	Close monitoring and screening are recommended for breeding programs and healthcare routines.
Stage B1	Asymptomatic dogs with mitral regurgitation, accompanied by absent of or minimal changes in cardiac structure that can be visualised using echocardiography or thoracic radiography.	Progress of cardiac remodelling should be checked every once to twice annually via echocardiography. Treatment plans should be devised based on individual cases.
Stage B2	Asymptomatic dogs with mitral regurgitation and morphological changes to the heart fulfilling criteria of cardiomegaly.	Commencement of treatment if all criteria are met.
Stage C	Dogs that demonstrate cardiac remodelling resulting in clinical signs of heart failure that medical treatment can successfully control.	Hospitalisation may be required based on the progression of the disease. In chronic cases, owner compliance is important since treatment is lifelong.
Stage D	Dogs with clinical signs contributing to heart failure that develop failure or are refractory to treatment strategies prescribed.	Introduction of new treatment plans to target further complications of heart failure as well as increasing dosages for drugs used to treat Stage C patients. Constant monitoring should be done for potential treatment side effects.

2.5 Diagnosis of DMVD

Auscultation is a convenient method to rule in DMVD despite its lack of sensitivity. A systolic murmur progresses with increasing severity from a systolic click heard loudest at the left cardiac apex (Häggström *et al.*, 2004; Ljungvall *et al.*, 2009; Borgarelli and Häggström, 2010).

Echocardiography is required for confirmative diagnosis of DMVD and is more sensitive to detect earlier stages of DMVD that may not have morphological alterations. Thickened leaflets and mitral regurgitation can be observed. (Häggström *et al.*, 2004).

Radiography acts as a supplement for diagnosis, utilising VHS and VLAS to detect the presence of cardiomegaly and left atrial enlargement, respectively. In the absence of echocardiography, more stringent radiographic criteria are required to diagnose DMVD (Keene *et al.*, 2019).

Cardiac biomarkers N-terminal fragment B-type natriuretic peptide (N.T.-proBNP) from myocardial stress and cardiac troponin due to myocardial injury are commonly used in the veterinary field, with commercial test kits available. Elevated concentrations of NT-proBNP can differentiate the origin of respiratory clinical signs (Oyama, 2013).

Other information, such as blood pressure and radiographic images during the disease's beginning, can be helpful in ruling out differential diagnoses unrelated to cardiac issues. With the high prevalence among geriatric dogs and renal failure as a potential side effect due to extensive diuretics usage, a complete clinical database on complete blood count and serum biochemistry can be useful (Creevy *et al.*, 2019; Keene *et al.*, 2019).

2.6 Treatment and management of dogs with DMVD

Based on the guidelines put forth by the ACVIM, only dogs with DMVD stages B2 and above warrant treatment (Keene *et al.*, 2019). There are contrasting opinions suggesting the judgement to prescribe pharmacological treatments should be done by

assessing cases individually, illustrating the benefits of ACE-i and pimobendan in prolonging the time towards the onset of CHF and cardiac-related deaths (Pouchelon *et al.*, 2008; Boswood *et al.*, 2016).

Hitherto, treatments have focused on the consequences of mitral insufficiency rather than valvular lesions (Häggström *et al.*, 2004). Treatments, can be differentiated into emergency treatments where the patient is experiencing acute clinical signs such as life-threatening pulmonary oedema or chronic treatment that must be conducted at home (Keene *et al.*, 2019).

Common pharmacological treatments for DMVD include inodilators such as pimobendan. As an inotropic drug, it inhibits phosphodiesterase III, an enzyme that metabolises cyclic adenosine monophosphate responsible for regulating calcium required for cardiac contractility (Boularan and Gales, 2015). This action improves cardiomyocytes' sensitivity to calcium, increasing contractility without requiring more oxygen. Pimobendan also has vasodilation functions on the arteries and veins (Plumb, 2011).

In addition, ACE-i such as enalapril, benazepril and imidapril interferes with the renin-angiotensin-aldosterone system (RAAS), despite different pharmacological actions all inhibits the formation of Angiotensin II that can cause functional and morphological changes of the cardiovascular system (Häggström *et al.*, 2009; Plumb, 2011; Riviere and Papich, 2018).

Diuretics, such as furosemide and spironolactone alleviate pulmonary oedema by decreasing tendency for fluid accumulation. Adjunctive therapy can be added to the treatment plan to alleviate clinical signs, often for coughing, by using bronchodilators

or cough suppressants. As for pulmonary hypertension, sildenafil was demonstrated to provide relief (Strickland, 2015).

Supplements can aid in maintaining cardiac function, such as Coenzyme Q10 and Vitamin E, which provide antioxidant protection and improve cardiac cell metabolism (Smith *et al.*, 2015).

ACVIM has suggested surgical repair via mitral annuloplasty and chordal replacement as a plausible treatment to maintain mitral valve function for patients in advanced Stage B2 up to Stage C, less so in Stage D due to the increased risks. However, studies are meagre due to affordability, ethical issues and difficulties in performing cardiac procedures on small dogs (Uechi, 2012; Mizuno *et al.*, 2013; Keene *et al.*, 2019).

Less invasive methods such as dietary changes via salt restriction, can also be practised. Dogs given special cardiac diets have improved cardiac sizes, showing a decrease in left atrial and ventricular size (Rush *et al.*, 2000; Freeman *et al.*, 2006). In addition, attention should be given to maintaining sufficient calorie and protein intake in patients to prevent cardiac cachexia or anorexia, which may be a potential treatment side effect (Keene *et al.*, 2019).

2.7 Quality of life

There are no clear guidelines for QoL evaluation in animals as of current. In essence, it is an amalgamation of mental and physical well-being (McMillan, 2000; Fulmer *et al.*, 2022).

Assessments performed are from the perspective of proxies, as animals cannot communicate their feelings verbally, referred to as observer-reported outcomes

(Fulmer *et al.*, 2022). However, the lack of training and experience in medical and behavioural knowledge can often lead to misinterpretation or missing specific critical criteria demonstrating their status of QoL (Abresch *et al.*, 2009; United States Food and Drug Administration, 2009). Furthermore, the QoL assessment may differ between what proxies perceive and what the individual assessed truly feels, leading to an over- or underestimation especially when subjective aspects such as emotions are involved (McCusker *et al.*, 1984; Mariti *et al.*, 2012).

The involvement of veterinarians in QoL remains limited to the animal's health status, commonly revolving around activity level, demeanour, and appetite (Fulmer *et al*., 2022). Disease-focused assessments will also include common clinical signs, such as the Functional Evaluation of Cardiac Health (FETCH) Questionnaire for Dogs, which considers the respiratory signs shown by dogs with heart conditions (Freeman *et al.*, 2005).

3.0 Materials and methods

3.1 Data collection

This retrospective cohort study was conducted at the University Veterinary Hospital (UVH) of Faculty of Veterinary Medicine (FPV). The clinic case log book was manually screened for dog patients diagnosed with DMVD between 2014 to 2023. The case file numbers of each dog patient were recorded, and the case files were manually retrieved and reviewed.

Information collected includes patient signalment, the stage of DMVD, treatment given, QoL variables, which include clinical findings and radiographic evidence of cardiac disease. The case history of each patient was inspected. Any concurrent diseases and medications, both cardiogenic and non-cardiogenic, were recorded.

QoL-related criteria were recorded for pre- (day-0) and post-treatment (day-60, day-180). The QoL variables based on clinical signs, thoracic radiography and well-being were evaluated during each examination (at pre-treatment; day-0 and post-treatment; day-60 and day-180)

3.2 Inclusion criteria

The inclusion criteria of patients recruited include i) dog patients diagnosed with DMVD stage C and stage D, ii) retrievable patient file records with complete patient signalment, iii) available information of physical examination, echocardiography and thoracic radiography pre- and post-treatment. Dog patients with other concurrent diseases/illnesses were excluded from the study as it may affect the assessment of QoL in this study that is related explicitly to DMVD.

Clinical diagnosis of DMVD was made based on echocardiography performed. Morphological characteristics include thickening of the mitral valve apparatus, enlargement of the left atrium and left ventricle, and left atrial to aortic root (LA/Ao) ratio≥1.6 in the right parasternal short axis view. Left ventricular internal diameter during diastole (LVIDd) normalised to patient body weight measured during M mode should also display measurement ≥1.7.

3.3 Patient signalment

Patient signalment, including age, breed, size, sex, and body weight were recorded.

The age of dogs was further categorised loosely referencing the 2019 American Animal Hospital Association (AAHA) Canine Life Stage Guidelines into two groups, taking into account the expected age of dogs affected by DMVD, which were adult (1- 7 years old) and senior (7 years old and over).

The breed of dogs was recorded and further grouped based on small or medium size. The sex of the affected dogs was recorded as male or female. The body weight was noted for all the three-time points.

3.4 Patient treatment

Treatments that were prescribed throughout the 180 days were noted. The recorded treatment regimes consist of only inodilators (pimobendan), ACE-i (benazepril, enalapril, imidapril) or both inodilators and ACE-i.

3.5 Quality of life variables

For QoL variables, the information was collected from the file where the owner was queried on the signs and symptoms they noted. Physical examination findings by the veterinarian on the case were noted.

DMVD-related characteristics were recorded based on protocols utilised in QUEST, EPIC and BENCH studies (Boswood *et al.*, 2018; Goldsmith *et al.*, 2001; Häggström *et al.*, 2008, 2013).

The patient QoL was assessed based on three categories: (i) well-being, clinical signs, and thoracic radiograph. For the well-being, it was further divided into demeanour (lethargy), appetite and exercise intolerance. The clinical signs were categorised into respiratory and circulatory. Respiratory variables comprised dyspnoea, coughing, panting and abdominal breathing. Circulatory variables included cyanosis and syncope.

All the thoracic radiography was retrieved. The presence of cardiomegaly was assessed based on the measurement of the VHS of the heart on the right lateral thoracic view. VHS was measured by drawing a long axis extending from the carina to the apex, followed by a short axis perpendicular to the long axis between the ventral juncture of the left atrium and the caudal vena cava. Lengths of both axes are measured against the vertebrae, starting from the fourth thoracic vertebrae and recorded as the number of vertebrae where this line passes through. Hearts with measurements above 10.5 are above the normal reference range of 9.7 ± 0.5 and thus considered enlarged. VLAS was used for the detection of left atrial enlargement. On the same lateral thoracic radiograph, a line is drawn from the ventral part of the carina, passing the caudal portion of the left atrium and extending to the dorsal border or the vena cava. The length of this line is compared to the vertebrae in an identical manner to obtain the measurement of VHS (Poteet, 2015; Keene *et al.*, 2019).

3.6 Scoring system for QoL variables

Each of the QoL variables was further given a score modified after the protocol utilised in the QUEST study conducted by Häggström (Häggström *et al.*, 2013) (refer Table 2)

Table 2: Quality of life scoring system

Variable	Score	Description
Appetite	1	Increased
	2	Normal
	3	Decreased (2/3 normal)
	4	Markedly decreased (<2/3 normal)
Lethargy	1	Alert, responsive
	2	Mildly depressed
	3	Moderately depressed
	4	Minimally responsive
	5	Unresponsive
Exercise intolerance	1	Dog moved around with ease, and was able to fully exercise
	2	Dog moved around with ease, not able to fully exercise; ability to run reduced
	3	Dog was less active than normal, moved around a few times per day, avoided long walks
	4	Dog was inactive and would only get up to eat, drink, or urinate
Dyspnoea	1	None
	2	Episodes of open-mouth breathing
	3	Consistent open mouth breathing warrants oxygen therapy
Cough	1	None
	2	Occasional (a few times a week)
	3	Frequent (a few times a day)
	4	Persistent (frequently during the day)
Panting	1	Present only after vigorous exercise or on very hot days
	2	Present only after excitement and mild exertion
	3	Present almost all the time
Abdominal breathing	1	None
	2	Present
Cyanosis	1	None
	2	Present
Syncope	1	None
	2	Present

3.7 Statistical analysis

Information and data collected were tabulated using Microsoft Excel. Data analysis was performed using Statistical Package for the Social Sciences (SPSS). The data collected was tested for normality.

Descriptive analysis was performed for all variables during different study time points (day-0, -60, and -180). Kolmogorov Smirnov's test was used to assess the normality of each data group. Normally distributed data was expressed in the form of mean, whereas non-normally distributed data was expressed in the form of median.

Friedman's test, followed by the post-hoc Conover test, assessed statistically significant differences between each time point.

To test for differences between treatment plans prescribed (inodilator, ACE-i, both; inodilator and ACE-i), the values collected from QoL of day-0, -60, and -180 were summarised using the time-weighted average. This was done using the area under the curve (AUC) with a baseline of 0 divided by its total time interval from the first to the last observation (Häggström *et al.*, 2013). Kruskal Wallis test was used to analyse Stage C patients with three different treatment plans, and Mann Whitney test for Stage D dogs with two treatment regimes. Significant results were subjected to post-hoc analysis by using Dunn's test.

Results with P values < 0.05 were considered statistically significant.

4.0 Results

A total of 155 dogs diagnosed with DMVD in stages C and D were included in the study for analysis. Only six dogs were excluded from further analysis due to violation of the inclusion criteria: inconsistent revisits (n=2), incomplete post-treatment information (n=1), and three dogs had yet to reach the desired endpoint of 180 days for data collection. A total of 149 DMVD dogs were evaluated for the effects of the prescribed treatment and QoL characteristics.

Regarding radiographic variables, four DMVD dogs were excluded due to insufficient radiographic information. The efficacy of different pharmacological treatments and the QoL relationship on radiographic evidence were analysed.

4.1 Patient signalment

Shih Tzu was the most commonly presented breed for DMVD at 34.20% out of the dogs recruited. Most dogs sampled were small breeds, accounting for 79.90% of the total dogs. The remaining 20.10% of dogs analysed were medium breeds.

The dogs sampled range from 2 to 18 years old, with an average age of 10. A total of 89.90% of the dogs analysed were senior dogs, with the remaining 10.10% being adults.

The body weight of all dogs sampled ranges from 1.30 kg to 25.40 kg, with an average of 6.40 kg. Male dogs are the most recruited, consisting of 51.00% of all dogs sampled.

The majority of the dogs diagnosed with DMVD were at Stage C at 67.80%, and the remaining 32.20% of the dogs were Stage D DMVD. (Table 3)

Table 3: Patient signalment of dogs diagnosed with DMVD (n= 149)

Patient signalment	Categories	No. of canines sampled, n	Percentage (%)
Size	Small	119	70.90%
	Medium	30	20.10%
Breed	Cavalier King Charles Spaniel	1	0.70%
	Chihuahua	3	2.00%
	Jack russell terrier	2	1.30%
	Maltese	5	3.40%
	Miniature pinscher	8	5.40%
	Miniature schnauzer (s)	3	2.00%
	Mix (s)	2	1.30%
	Pekingese	7	4.70%
	Pomeranian	8	5.40%
	Poodle	18	12.10%
	Shih tzu	51	34.20%
	Silky terrier	3	2.00%
	Standard poodle	1	0.70%
	Terrier	3	2.00%
	Toy poodle	4	2.70%
	American cocker spaniel	2	1.30%
	Basset hound	1	0.70%
	Beagle	1	0.70%
	Cocker spaniel	5	3.40%
	English cocker spaniel	2	1.30%
	Local	10	6.70%
	Miniature schnauzer (m)	3	2.00%
	Mix (m)	2	1.30%
	Schnauzer	1	0.70%
	Spitz	2	1.30%
	Springer spaniel	1	0.70%
Age group	Senior	134	89.90%
	Adult	15	10.10%
Sex	Male	76	51.00%
	Female	73	49.00%
DMVD	Stage C	101	67.80%
	Stage D	48	32.20%

4.2 Effect of Treatment

The effect of treatment was tested with the following parameters: body weight, appetite, lethargy, exercise intolerance, dyspnoea, coughing, panting, abdominal breathing, cyanosis and syncope.

There was a significant effect ($p < 0.05$) before and after treatment for appetite, lethargy, exercise intolerance, dyspnoea, coughing, panting, abdominal breathing, and syncope. Out of the variables, body weight and cyanosis did not portray significant differences before and after treatment. There was a significant difference in well-being, respiratory and circulatory variables between days 0, 60 and 180 after medical therapy. (Table 4)

Table 4: Summary of treatment effect on QoL variables

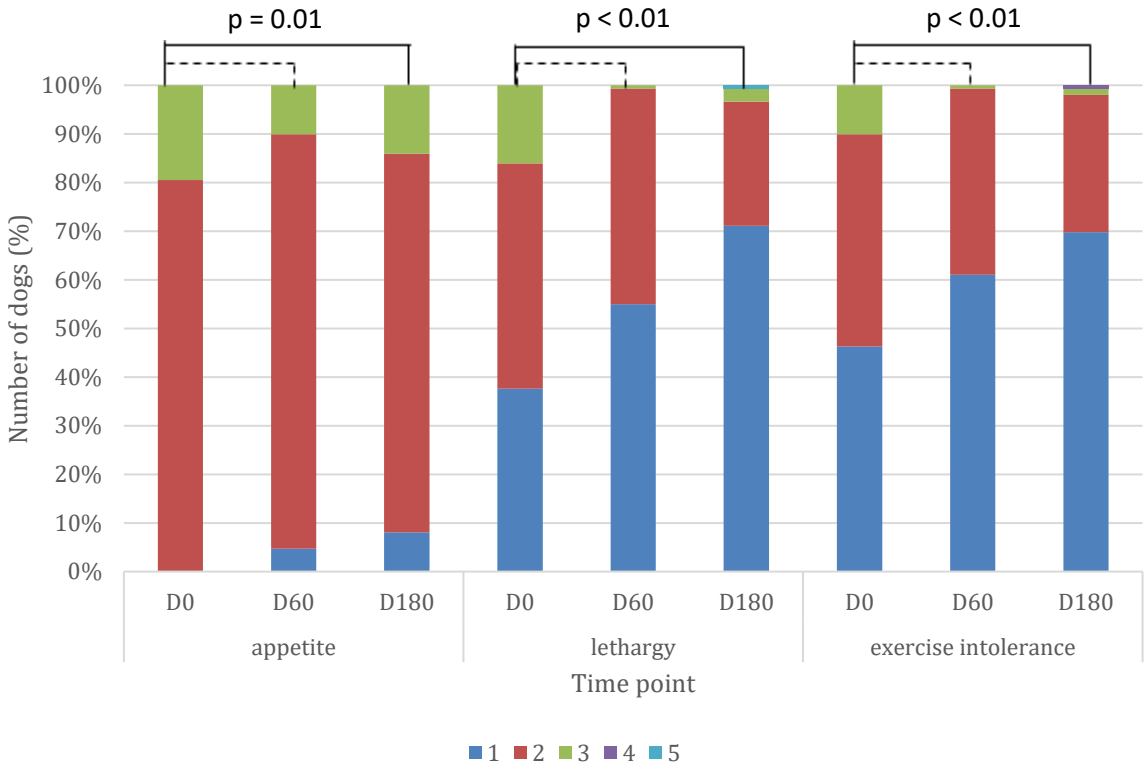
P values marked with * indicate significant statistical difference

	Variable	Days	Median	IQR	F	P value	Conover Post Hoc test (Days)
Well-being	Body weight (kg)	0	6.6	2.66-10.54	1.21	0.30	
		60	6.4	2.46-10.34			
		180	6.4	2.46-10.34			
	Appetite	0	2	1.60-2.40	5.13	0.01*	60, 180
		60	2	1.62-2.38			0
		180	2	1.53-2.47			0
	Lethargy	0	2	1.30-2.70	46.67	<0.01*	60,180
		60	1	0.49-1.51			0,180
		180	1	0.40-1.60			0,60
	Exercise intolerance	0	2	1.34-2.66	27.94	<0.01*	60,180
		60	1	0.50-1.50			0
		180	1	0.46-1.54			0
Respiratory variables	Dyspnoea	0	1	0.52-1.48	15.98	<0.01*	60,180
		60	1	0.68-1.32			0
		180	1	0.61-1.39			0
	Coughing	0	3	2.26-3.74	67.53	<0.01*	60,180
		60	2	1.16-2.84			0
		180	2	1.06-2.94			0
	Panting	0	2	1.43-2.57	6.00	<0.01*	60,180
		60	2	1.50-2.50			0
		180	2	1.45-2.55			0
	Abdominal breathing	0	1	0.57-1.43	14.56	<0.01*	60,180
		60	1	0.76-1.24			0
		180	1	0.70-1.30			0
Circulatory variables	Cyanosis	0	1	0.75-1.25	2.86	0.06	
		60	1	0.88-1.12			
		180	1	0.80-1.20			
	Syncope	0	1	0.68-1.32	5.73	<0.01*	60,180
		60	1	0.79-1.21			0
		180	1	0.80-1.20			0

Patient well-being

For patient well-being, significant differences are present. Patients have statistically significant improvement in appetite, lethargy and exercise intolerance, with the number of patients with lower scores (score 1 and score 2) increasing for day-60 and day-180 compared to day-0. However, for all patient well-being parameters, a slight increase in patients having a worse score (score 3) on day-180 compared to day-60 was noted. (Figure 1)

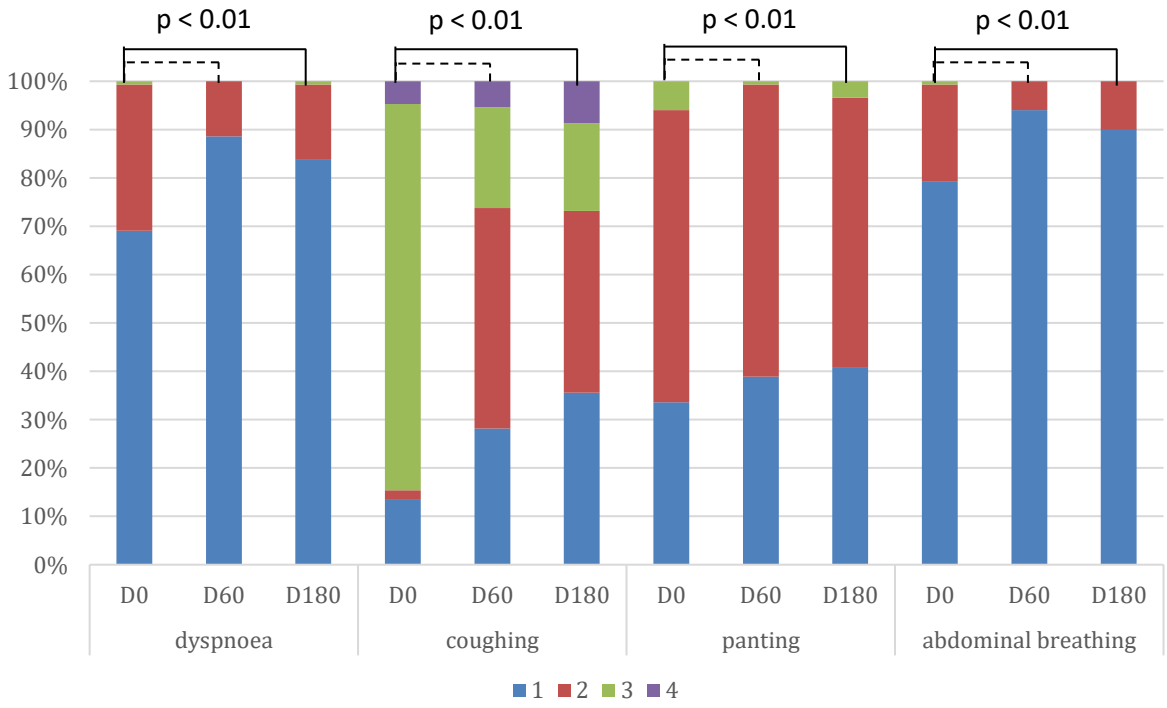
Figure 1: Bar chart of well-being scores of dogs in the study



Respiratory variables

For all respiratory parameters, dogs that received treatment (day-60, day-180) demonstrated significant improvement in scores for dyspnoea, coughing, panting and abdominal breathing compared to before treatment (day-0). There was a slight worsening of scores among dogs on day-180 for all variables, with an increase of dogs showing a score of 3 for dyspnoea and panting, 4 for coughing and 2 for abdominal breathing compared to day-60. (Figure 2)

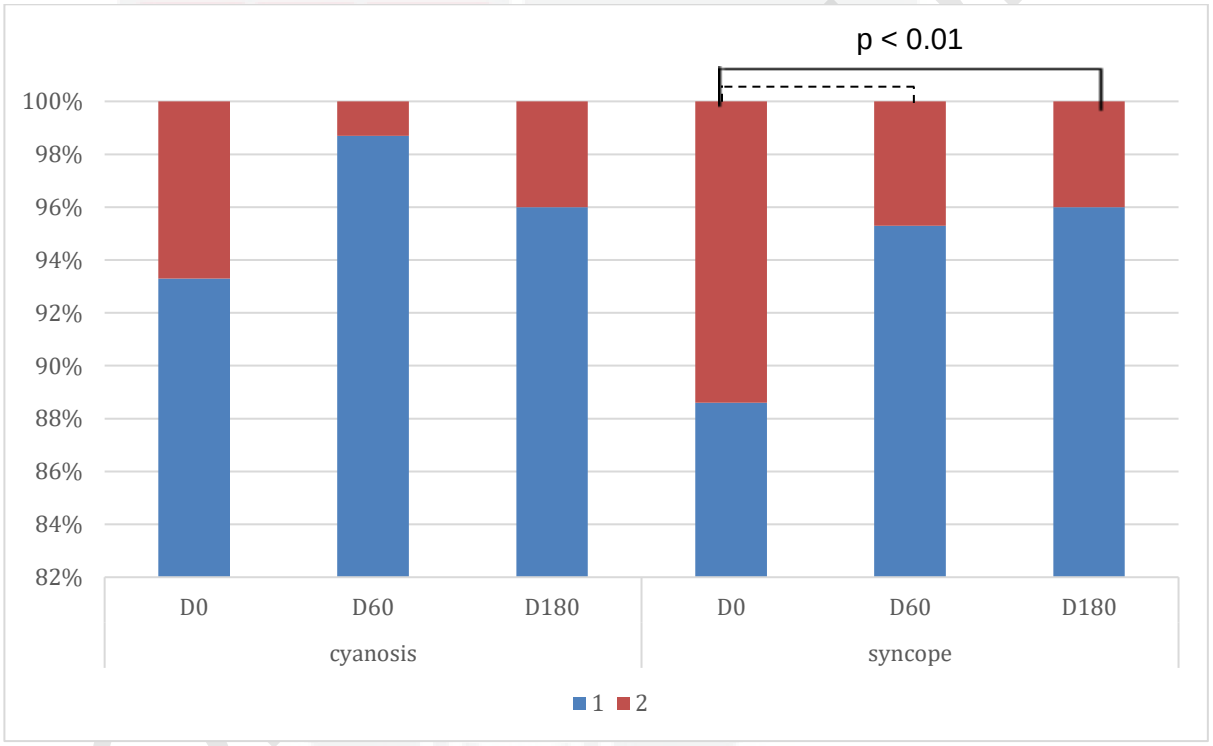
Figure 2: Bar chart of respiratory variable scores of dogs in the study



Circulatory variables

The number of dogs with cyanosis decreased after commencement of treatment on day-60 and day-180 compared to day-0. Patients that have syncope reduced significantly after treatment. (Figure 3)

Figure 3: Bar chart of circulatory variable scores of dogs in the study



4.3 Differences among Treatments

The dogs were divided into 3 groups based on the type of treatment prescribed: ACE-i, inodilators or both (ACE-i and inodilator). In this group of dogs, majority (55.30%) of the DMVD dogs were prescribed ACE-i, followed by 33.60% with both (ACE-i and inodilator), whereas the remaining 13.40% were given inodilator only. (Table 5)

The effect of treatments on dogs with different DMVD stages is summarised in tables 6, 7, 8 and 9.

Table 5: Treatment groups (n= 149)

Treatment	Frequency	Percentage
Both[1]	50	33.60%
ACE-i	79	53.00%
Inodilator	20	13.40%
Total	149	100.00%

[1] Both, treatment with ACE-i and inodilator

Table 6: Treatment effect on dogs diagnosed with DMVD Stage C (n= 101)

P values marked with * indicate significant statistical difference

	Variable	Treatment	n	Median	H	df	X^2	P value
Well-being	Body weight (kg)	ACE-i	59	6.90	4.41	2	4.41	0.11
		Inodilator	20	6.32				
		Both[1]	22	6.03				
	Appetite	ACE-i	59	2.00	1.99	2	2.88	0.24
		Inodilator	20	2.00				
		Both[1]	22	2.00				
	Lethargy	ACE-i	59	1.67	4.00	2	4.24	0.12
		Inodilator	20	1.08				
		Both[1]	22	1.17				
	Exercise intolerance	ACE-i	59	1.17	0.51	2	0.57	0.75
		Inodilator	20	1.17				
		Both[1]	22	1.17				
Respiratory variables	Dyspnoea	ACE-i	59	1.00	4.39	2	5.94	0.05
		Inodilator	20	1.00				
		Both[1]	22	1.17				
	Coughing	ACE-i	59	2.17	0.04	2	0.05	0.98
		Inodilator	20	2.00				
		Both[1]	22	1.92				
	Panting	ACE-i	59	2.00	1.99	2	2.20	0.33
		Inodilator	20	1.83				
		Both[1]	22	1.17				
	Abdominal breathing	ACE-i	59	1.00	0.10	2	0.20	0.90
		Inodilator	20	1.00				
		Both[1]	22	1.00				
Circulatory variables	Cyanosis	ACE-i	59	1.00	0.52	2	1.65	0.44
		Inodilator	20	1.00				
		Both[1]	22	1.00				
	Syncope	ACE-i	59	1.00	0.13	2	0.49	0.78
		Inodilator	20	1.00				
		Both[1]	22	1.00				

[1] Both, treatment with ACE-i and inodilator

Table 7: Treatment effect on dogs diagnosed with DMVD Stage D (n= 48)

P values marked with * indicate significant statistical difference

	Variable	Treatment	n	Median	U	Z	P value
Well-being	Body weight	ACE-i	20	5.13	155.00	-2.61	0.01*
		Both[1]	28	7.55			
	Appetite	ACE-i	20	2.00	260.50	-0.45	0.66
		Both[1]	28	2.00			
	Lethargy	ACE-i	20	1.50	261.00	-0.41	0.68
		Both[1]	28	1.50			
	Exercise intolerance	ACE-i	20	1.42	256.50	-0.51	0.61
		Both[1]	28	1.67			
Respiratory variables	Dyspnoea	ACE-i	20	1.00	270.50	-0.22	0.83
		Both1	28	1.00			
	Panting	ACE-i	20	2.00	223.00	-1.36	0.18
		Both[1]	28	2.00			
	Abdominal breathing	ACE-i	20	1.00	267.00	-0.33	0.75
		Both[1]	28	1.00			
Circulatory variables	Cyanosis	ACE-i	20	1.00	230.00	-1.97	<0.05*
		Both[1]	28	1.00			
	Syncope	ACE-i	20	1.00	270.00	-0.28	0.78
		Both[1]	28	1.00			

	Variable	Treatment	n	Mean	t	df	X^2	P value
Respiratory variables	Coughing	ACE-i	20	2.33	0.81	46	1.72	0.42
		Both[1]	28	2.50				

[1] Both, treatment with ACE-i and inodilator

Table 8: Treatment effect on radiographic evidence of dogs diagnosed with DMVD Stage C (n= 101)

P values marked with * indicate significant statistical difference

Variable	Treatment	n	Mean/ Median	F ratio/ H	df	X^2	P value
VHS	ACE-i	37	10.42	3.60	2	7.01	0.03*
	Inodilator	15	10.60				
	Both[1]	19	11.12				
VLAS	ACE-i	37	2.02	3.24	2	3.22	0.20
	Inodilator	15	2.12				
	Both[1]	19	2.37				

[1] Both, treatment with ACE-i and inodilator

Table 9: Treatment effect on radiographic evidence of dogs diagnosed with DMVD Stage D (n= 48)

P values marked with * indicate significant statistical difference

Variable	Treatment	n	Mean	t	df	P value
VHS	ACE-i	16	11.62	0.20	40	0.84
	Both[1]	26	11.70			

Variable	Treatment	n	Median	U	Z	P value
VLAS	ACE-i	16	2.72	177.00	-0.80	0.42
	Both[1]	26	2.93			

[1] Both, treatment with ACE-i and inodilator

4.4 Correlation between VHS, VLAS and QoL variables

Spearman's Rho test was performed to determine the correlation between measurements of the heart based on radiographic findings and the QoL variables. VHS displayed no significant correlation with any QoL variables. (Table 10)

Table 10: Correlation between VHS to QoL variables of dogs with DMVD (n= 145)

P values marked with * indicate significant statistical difference

Radiographic measurement	QoL variables		Spearman's rho	P value
VHS	Well-being	Body weight (kg)	0	0.98
		Appetite	-0.05	0.59
		Lethargy	0.01	0.92
		Exercise intolerance	-0.09	0.26
	Respiratory variables	Dyspnoea	0.15	0.08
		Coughing	0.03	0.74
		Panting	0.13	0.11
		Abdominal breathing	0.16	0.05
	Circulatory variables	Cyanosis	-0.05	0.57
		Syncope	0.15	0.08

In addition, VLAS is significantly correlated to abdominal breathing (p= 0.016) and syncope (p= 0.015). (Table 11)

Table 11: Correlation between VLAS to QoL variables of dogs with DMVD (n= 145)

P values marked with * indicate significant statistical difference

Radiographic measurement	QoL variables		Spearman's rho	P value
VLAS	Well-being	Body weight (kg)	-0.08	0.32
		Appetite	-0.06	0.45
		Lethargy	-0.08	0.37
		Exercise intolerance	-0.10	0.22
	Respiratory variables	Dyspnoea	0.10	0.25
		Coughing	0.11	0.17
		Panting	0.08	0.37
		Abdominal breathing	0.20	0.02*
	Circulatory variables	Cyanosis	-0.04	0.68
		Syncope	0.20	0.02*

5.0 Discussion

Similar to previous studies, this study showed that DMVD is highly prevalent in small breeds, especially seniors. In the UVH-UPM, FPV from 2014 to 2023, Shih Tzu was the most common breed presented for DMVD, which its breed predisposition is supported by limited studies (Serfass *et al.*, 2006).

However, the evidence of sex predisposition in males was not strongly demonstrated in this study. Several breed-specific studies demonstrated that sex does not strongly influence DMVD prevalence, but a faster progression of clinical signs is noted in males (Lundin and Kvart, 2010; Lewis *et al.*, 2011). Hence, male dogs had a slightly higher prevalence than females and were reported in this study to be diagnosed at a younger age, between 2 and 17 years old, compared to females between 3 to 18 years old. In our study, more females were presented at a younger age (8 years old) in 12 dogs than males (10 years old) in 17 dogs, and the findings were in contrast with several studies (Olsen *et al.*, 1999; Häggström *et al.*, 2004; Lundin and Kvart, 2010).

Treatment in this study refers to medical therapy that was prescribed as a long-term management plan for the dogs diagnosed with DMVD. This study investigated three QoL components related to health status and clinical signs, which were well-being (body weight, appetite, lethargy, exercise intolerance), respiratory variables (dyspnoea, coughing, panting, abdominal breathing) and circulatory variables (cyanosis, syncope).

QoL scores of dogs with CHF clinical signs improved when treated with ACE-i, inodilator or both medications over 180 days. Dogs showed better scores after treatment (day-60 and day-180) for well-being (appetite, lethargy, exercise intolerance), respiratory variables (dyspnoea, coughing, panting, abdominal breathing) and circulatory variables (syncope). As long as dogs were treated, treatment positively improved QoL. A study

observed that QoL parameters such as appetite, demeanour, exercise tolerance and coughing significantly improved with treatment, but this difference is within treatment groups itself. Reports by owners of the placebo group also showed significant improvement in demeanour and exercise intolerance (Boswood *et al.*, 2018). Another study reported that there were significant differences between treatment and placebo groups, with improvements in exercise intolerance and global clinical condition in favour of the ACE-i group during the early stages of the study on day 28 [BENCH (BENazepril in Canine Heart disease) Study Group, 1999]. Veterinarian assessment of the clinical signs may help to mitigate the potential placebo effect that may be perceived by the owner when assessing the QoL of their dogs.

Exceptions of the beneficial effects of treatment were seen. The body weight of the dogs and cyanosis were not positively improved. Despite already setting a criterion for recruiting only small breeds and certain medium breeds, there is still a variation in breeds and sizes, causing differences in body weight and their normal ranges. In this study, the median was 6.4 kg, with the smallest dog recruited being 1.30 kg, while the heaviest dog was 25.40 kg. The variation could have been too broad to allow any statistical difference to be observed. As for cyanosis, the knowledge of dog owners can easily influence the understanding or ability to identify cyanosis, which may vary between owners and their veterinarians (Noble *et al.*, 2019). Skin and mucous pigmentation may obscure the colour changes related to poor oxygen uptake. Even the surrounding lighting may play a significant role in detection (Scully, 2014; Smith *et al.*, 2015). Sometimes, the presentation of cyanosis can be affected by stress and excitatory conditions of the dog. Dogs that are easily agitated may have increased cyanosis, thereby raising the likelihood of cyanosis being observed by the owners. During consultation, dogs may be less likely

to display cyanosis when examined by veterinarians due to restriction and reduction in activity level, as the dogs are less likely to perform vigorous exercise during these events.

After treatment, there is a slight increase in worse scores on day-180 compared to day-60. This worsening of QoL is less likely related to the efficacy of drugs and more to the rise in disease severity. As DMVD progresses, dogs tend to be refractory towards treatment protocols given.

Worsening of QoL scores can be related to the natural progression in severity of the disease, and reduced functionality of multiple organs simply due to natural ageing or side effects of medications used in the long run. The drugs evaluated in this study were described to exert undesirable effects. For instance, ACE-i can adversely affect myocardial protein metabolism, while inodilators cause negative effects on cardiac function and morphology in asymptomatic dogs (Lombard *et al.*, 2006; Chetboul *et al.*, 2007). ACE-i and inodilators were also shown to have side effects on the gastrointestinal system (Plumb, 2011). All these side effects emphasise the weight and caution that must be taken when formulating treatment protocols.

The benefit of treatment seems to allow for the improvement of QoL and ease of management of dogs with DMVD; however, there is a need to understand which medication effectively maintained the DMVD dogs at stages C and D as the dog owners can easily monitor clinical signs. Therefore, a comparison of effects on QoL between different medical therapies was made by first separating the recruited dogs based on stages of DMVD. In this study, Stage C dogs had a total of three different treatment regimes: ACE-i, inodilator or both (ACE-i and inodilator), whereas Stage D dogs had two groups consisting of ACE-i alone or ACE-i with inodilator.

The average QoL scores for Stage C dogs are similar despite being prescribed with any one of the three different treatment plans. Findings from Häggström *et al.* (2013) were similar, with further observations reporting the beneficial effects of inodilators compared to ACE-i. Inodilators could prevent the QoL of DMVD dogs from exacerbating for a longer time before requiring necessary treatment intensification via increasing dosages of present drugs or adding other drugs (Häggström *et al.*, 2013). The findings were at odds with research conducted by Smith *et al.* (2005) that notes ACE-i treatment alone predisposes dogs to a higher likelihood of adverse heart failure outcomes related to mobility and demeanour.

Other research also stated that patients with inodilator included in their treatment regime take a longer time to reach the treatment endpoint, which is defined as death, euthanasia of cardiac origin or treatment failure (Lombard *et al.*, 2006; Häggström *et al.*, 2008). Inodilators were recorded to have better efficacy in other aspects not observed in this study. Dogs with treatment plans involving inodilators had a higher rectal temperature, serum sodium concentration, packed cell volume (PCV) and total protein concentration (TPC). A higher value of these elements was associated with a better prognosis (Häggström *et al.*, 2013). Inodilators were also found to improve heart function in terms of cardiac output, systolic function and ejection fraction (Lombard *et al.*, 2006; Häggström *et al.*, 2013; Häggström *et al.*, 2013).

As for Stage D dogs, ACE-i had better efficacy in improving the body weight of patients when compared to dogs prescribed both ACE-i and inodilator. A similar finding was observed for cyanosis as well. ACE-i counteracts against the RAAS, reducing vasoconstriction and reabsorption of sodium and chloride (Häggström *et al.*, 2009; Strickland, 2015). Decreased tendency for fluid retention in blood vessels allows for a

lower interstitial pressure, mitigating the risks of fluid leakage into air spaces that will cause pulmonary oedema (Lee and Drobatz, 2004). Consequently, the gaseous exchange can occur efficiently, therefore reducing instances of cyanosis—results illustrating that ACE-i as a more effective drug corroborates several studies. Elements of body weight and cyanosis were not evaluated in these studies specifically, but they displayed the superior effects of inodilators in improving clinical signs related to exercise intolerance, demeanour and respiration (Smith *et al.*, 2005; Lombard *et al.*, 2006; Häggström *et al.*, 2013).

Radiographic elements, such as VHS and VLAS, were also analysed in this study. In Stage C, ACE-i is more efficient in controlling cardiomegaly than inodilator alone and a combination of both inodilator and ACE-i. In Stage D, treatment effects on VHS and VLAS did not differ significantly between dogs given ACE-i alone and dogs with a combination of ACE-i and inodilator. The findings observed for Stage C dogs were at odds with findings reported by previous research stating that usage of inodilators was able to reduce heart size or maintain a lower VHS compared to ACE-i (Lombard *et al.*, 2006; Woolley *et al.*, 2007; Häggström *et al.*, 2013; Häggström *et al.*, 2013).

The variation in treatment efficacy between this study and previous studies comparing ACE-i and inodilator can be related to unequal sample sizes of treatment groups. The sizes of each treatment group in these studies did not possess great differences from one another, allowing for better comparison (Lombard *et al.*, 2006; Häggström *et al.*, 2008; Häggström *et al.*, 2013). For Stage C dogs, 59 patients were treated with ACE-i alone, whereas only 20 and 22 patients were treated with inodilators alone and a combination of both ACE-i and inodilators, respectively. The overrepresentation of dogs in the ACE-i group can lead to a higher likelihood of the appearance of beneficial effects.

Perhaps the usage of polypharmacy can be taken into account. Since this study focuses on comparing ACE-i and inodilators, the effects of other concurrent medications were not determined. The small sample size recruited for this study and ethical considerations when denying necessary treatment involving other medications that may alter the clinical signs assessed led to this potential cofounder. It can be argued that the integration between medications plays a role in variations between findings in this study and past literature. Improvement in QoL variables may not be solely contributed by the drugs evaluated. For instance, bronchodilators or cough suppressants may mask clinical signs of coughing. Diuretics, often a primary constituent in treatment strategies for cardiac cases, aid in reducing fluid accumulation in lung parenchyma and may also alleviate signs of coughing and other respiratory parameters. Dogs in one group could maybe have the added advantage in less severe clinical signs, which is an effect from other medications not accounted for in this study compared to the other, resulting in a better QoL score, which is then displayed as one drug more efficient in improving QoL than the other.

Additionally, the main goal of medical treatment is to reduce the amount of drugs required for maintaining QoL. Haggstrom *et al.* (2013) commented that the increased variety of drugs in a treatment regime adversely impacts owner compliance, administration errors, the cost required and stress associated with feeding dogs medications. Thus, despite belonging to the same DMVD stage classification, dogs prescribed ACE-i and inodilators together may have more severe clinical signs that warrant more medications than dogs using ACE-i or inodilators alone.

ACE-i alone may be insufficient to further maintain QoL due to inadequate response to the drug despite increased dosage, or further increases in dosage are deemed futile when the symptoms are refractory towards ACE-i. The addition of inodilators into the treatment

protocol can be justified by the decrease in cardiac functionality, thereby requiring the aid of inodilators to increase contractility for maintaining QoL. However, in this study, whether ACE-i or inodilator was not added to the treatment protocol when the dogs in DMVD stage C treated with either ACE-i or inodilator was not known.

Progressive severity of clinical signs could lead to further complications, such as cardiac cachexia, which is the wasting of muscles and a decrease in body weight despite a good appetite, causing drastic changes in body weight. Increasing cytokine levels and disrupted energy production worsen appetite and weight loss (Oyama, 2015). The possible side effects of drugs over an extended period can also accelerate weight loss either directly or indirectly through loss of appetite (Gompf, 2015).

As explained in non-significant differences regarding body weight before and after treatment, dogs still displayed variations in body sizes despite this study only limiting the inclusion criteria to small and medium breeds. Different dogs can have variations in chest conformation, which is stated by Buchanan (2000) for Miniature Schnauzers and Dachshunds differing in thorax length. The thoracic vertebrae also vary in height and length. Shih Tzus were found to have long thoracic vertebrae with a high T4 length-to-height ratio, leading to a lower average VHS. On the other hand, Schnauzers with shorter vertebrae can have normal VHS ranging up to 11 (Tangpakornsak *et al.*, 2023).

Given that most of the recruited population consists of Shih Tzus (34.20%), this may cause a reduction in the average VHS recorded, with a median VHS of 10.80, contradicting ACVIM guidelines classification. However, no VHS specifically for Shih Tzus were developed. Even among small-breed dogs, VHS can have different normal ranges. Therefore, breed-specific VHS was developed for several breeds, including but not limited to CKCS, Labrador Retrievers, Dachshunds, Boston Terriers, Boxers,

Bulldogs, Pomeranians, Pugs and Whippets (Buchanan and Bücheler, 1995; Lamb *et al.*, 2001; Bavegems *et al.*, 2005; Jepsen-Grant *et al.*, 2013; Taylor *et al.* 2020).

Another potential factor is that, unlike VLAS, which only requires a single measurement, VHS needs two measurements of the long and short axes, predisposing it to higher risks of compound errors than VLAS. Increases in VHS could signify that the dog has reached a very severe stage of DMVD, to a point where the ventricle shows dilatation and hypertrophy to compensate for the exacerbating mitral regurgitation (Abbott, 2015). Perhaps the dogs analysed in this study have yet to reach such severity to demonstrate a correlation between VHS and the clinical signs observed.

Essentially, VLAS refers to the dilation of the left atrium and is calculated similarly to VHS. This may also expose VLAS measurements to similar variations caused by chest conformation and thoracic vertebrae length. Efforts were taken to develop breed-specific VLAS, such as in Chihuahuas and CKCS (Puccinelli *et al.*, 2021; Bagardi *et al.*, 2022).

A correlation was found between VLAS, abdominal breathing and syncope, but it was a weak relationship. Mitral regurgitation can affect the left atrial size. As the regurgitant fraction increases, more stroke volume flows into the left atrium back into the lungs, as opposed to the systemic circulation via the aorta (Kittleson and Brown, 2003). As more blood backflows into the left atrium, the left atrial afterload increases, eventually resulting in volume overload and dilation of this heart chamber (Patel *et al.*, 2009). Relating to other hypotheses on the relationship between left atrial enlargement and the presentation of clinical signs, compression on the airway exerted by the dilated left atrium may compromise respiratory variables (Singh *et al.*, 2012; Gompf, 2015). The left mainstem bronchus between the left atrium and the left pulmonary artery is constricted by two opposing forces, causing a narrowing of the airway (Singh *et al.*, 2012). This leads to

respiratory distress, which is then displayed as abdominal breathing upon consultation, as the dog utilises abdominal muscles during exhalation to overcome the increased resistance.

Enlargement of the left atrium can be associated with more severe CHF clinical signs, such as pulmonary oedema. Mitral regurgitation results in decreased cardiac output, causing congestion and increased pulmonary pressure, combined with the RAAS that triggers an increase in blood volume by reabsorption of sodium and water, resulting in the interstitial pressure to exceed alveolar pressure. Fluid then leaks into the alveolar spaces from blood vessels to lung tissue. Large amounts of fluid in air sacs disrupt gaseous exchange and ventilation, causing breathing difficulties, also demonstrated as abdominal breathing (Lee and Drobatz, 2004; Strickland, 2015).

Since abdominal breathing serves to compensate for increased difficulties in breathing, other clinical signs or less severe methods such as dyspnoea, panting or coughing should, in theory, also demonstrate a correlation with VLAS. However, this study failed to demonstrate the relationship between VLAS and these QoL variables, and it could be speculated that these dogs were under treatment therapy. Several studies have made speculations on how left atrial size can lead to the degradation of respiratory variables, specifically coughing, but they have yet to be proven (Sisson *et al.*, 1999; Singh *et al.*, 2012; Gompf, 2015). As for the correlation between VLAS and syncope, increased regurgitation fraction reduces stroke volume and decreases cardiac output. Thus, cerebral blood flow is insufficient, increasing instances of syncope in DMVD dogs (Gompf, 2015).

No studies have determined the correlation between VLAS or left atrial enlargement with abdominal breathing or syncope. Research focuses on respiratory variables, exercise

intolerance or fatigue, as the primary clinical signs that are more reliable indicators of left-sided heart failure (Schober *et al.*, 2010; Ferasin *et al.*, 2013; Gompf, 2015).

6.0 Conclusion

Treatments using ACE-i, inodilators or both medications effectively improved QoL variables in small to medium-breed dogs diagnosed with Stage C or Stage D DMVD. After treatment, parameters that improved were appetite, lethargy, exercise intolerance, dyspnoea, coughing, panting, abdominal breathing and syncope.

In this study, dogs diagnosed with DMVD Stage C did not demonstrate QoL differences between treatment groups. Meanwhile, ACE-i showed better efficacy in controlling body weight and cyanosis for Stage D dogs.

Stage C dogs prescribed only ACE-i have a lower VHS than dogs given inodilators or both inodilators and ACE-i.

As for radiographic characteristics, this study demonstrates that VLAS can be used as a prognostic indicator for abdominal breathing and syncope.

7.0 Recommendations

Treatment of DMVD requires a complex integration of different medications to mitigate the severity of clinical signs. The inclusion of other medications that were used to control CHF can allow a more accurate assessment of the treatment effects of each specific drug. If possible, the study can be conducted on a larger scale with a bigger and more equal sample size. This allows for a better representation of treatment groups and breeds.

For observation of more apparent and long-term effects of pharmacological therapy on DMVD dogs, the time point of this study can be extended from 6 months to 1 year. Other aspects, such as survival time, time taken to reach different endpoints, and risk factors, could be considered to look at DMVD from a more holistic perspective.

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