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CENTRO UNIVERSITÁRIO DE LISBOA
FACULDADE DE MEDICINA VETERINÁRIA
MESTRADO INTEGRADO EM MEDICINA VETERINÁRIA

RETROSPECTIVE STUDY ON 163 CASES OF CANINE DILATED CARDIOMYOPATHY

Dissertação apresentada a provas públicas para a obtenção do grau de mestre em Medicina Veterinária, orientado por Professor Doutor Luís Lima Lobo

Pedro Machado, n.º 21805669

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VERSÃO FINAL

Dissertação defendida em provas públicas na Universidade Lusófona, Centro Universitário de Lisboa, no dia 10/04/2025, perante o júri, nomeado pelo Despacho de Nomeação n.º: 252/2025, de 26 de Março, com a seguinte composição:

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Abstract

Canine dilated cardiomyopathy (DCM) is a condition that can affect all heart chambers but usually is characterized by systolic and diastolic dysfunction, which in a severe stage leads to congestive heart failure or sudden death. The prevalence of this disease is higher in middle-aged male dogs of medium to giant breeds. The aetiology of DCM is normally idiopathic, but a few causes have been reviewed by the literature: nutritional, genetics, immunological, drugs and persistent tachycardia. Among the different diagnostic methods, echocardiography is the most reliable one, however, the definitive diagnosis requires histopathological analysis. The treatment of this pathology varies from each patient, but it is common the use of diuretics, positive inotropic drugs, beta-blockers, ace-inhibitors and antiarrhythmic drugs.

This dissertation is a retrospective study of 163 dogs diagnosed with DCM, between February 2001 and November 2024 at Hospital Veterinário do Porto, and the main goal is to characterize the disease in Portugal and compare the results with those published to date.

After analyzing the results, some differences were found regarding the clinical history, physical examination, echocardiographic measurements, estimated survival time and prognostic factors. The results are within what was expected when compared with the bibliographic review. However, due to the heterogeneity of the populations in the different studies, some results differed, particularly regarding breed prevalence. In this study, the Estrela Mountain Dog was the predominant breed.

Key-words: Dog/ Dilated cardiomyopathy/ Systolic dysfunction/ Congestive heart failure

Resumo

A cardiomiopatia dilatada canina é uma condição que pode afetar todas as câmaras cardíacas do coração, mas geralmente é caracterizada por uma disfunção sistólica e diastólica, que num estadio mais grave conduz à insuficiência cardíaca congestiva ou morte súbita. A prevalência desta doença é maior em cães machos de meia idade de raças médias a gigantes. A etiologia da cardiomiopatia dilatada é normalmente idiopática, mas algumas causas foram analisadas pela literatura podendo ser nutricional, genética, imunológica, medicamentosa e devido a taquicardia persistente. Entre os diferentes métodos de diagnóstico, a ecocardiografia é o mais confiável, no entanto, o diagnóstico definitivo só pode ser feito histopatológicamente. O tratamento desta patologia varia de paciente para paciente, mas é comum o uso de diuréticos, fármacos inotrópicos positivos, betabloqueadores, inibidores da ECA e medicações antiarrítmicas.

Este estudo retrospectivo analisou 163 casos de cães diagnosticados com cardiomiopatia dilatada entre fevereiro de 2001 e novembro de 2024 no Hospital Veterinário do Porto. O principal objetivo foi caracterizar a doença em Portugal e comparar os achados com a literatura existente. Foram avaliados dados relacionados com a história clínica, exame físico, achados ecocardiográficos, tempo de sobrevivência e fatores prognósticos.

Os resultados indicaram algumas diferenças em relação à prevalência racial, com destaque para o Cão da Serra da Estrela como a raça mais afetada. A análise ecocardiográfica revelou alterações compatíveis com a doença, incluindo aumento dos volumes sistólico e diastólico do ventrículo esquerdo, redução da fração de encurtamento e da fração de ejeção. O tempo de sobrevivência estimado variou consideravelmente, sendo influenciado pela presença de arritmias, insuficiência cardíaca congestiva e resposta ao tratamento.

Ademais, a análise estatística revelou correlações significativas entre alguns parâmetros ecocardiográficos e a sobrevivência dos pacientes. Cães com uma fração de ejeção e de encurtamento baixas apresentaram um prognóstico reservado, enquanto aqueles que tinham valores superiores demonstraram um aumento significativo na expectativa de vida. Além disso, o estadio da doença no momento do diagnóstico, também influenciou o tempo de sobrevivência, sendo que animais num estadio mais avançado com sinais de insuficiência cardíaca congestiva, obtiveram um pior prognóstico.

Apesar da concordância geral dos resultados deste estudo com a literatura internacional, observa-se que as diferenças na distribuição das raças acometidas podem ser atribuídas à população canina específica da região estudada. Adicionalmente, a heterogeneidade dos estudos publicados previamente e as diferenças metodológicas podem influenciar os resultados obtidos. Conclui-se que a cardiomiopatia dilatada continua a ser uma das principais cardiopatias em cães, com impacto significativo na qualidade de vida e sobrevivência dos animais acometidos. O diagnóstico precoce e o maneio adequado são essenciais para otimizar o prognóstico e melhorar a resposta ao tratamento. Estudos adicionais são necessários para aprofundar o conhecimento sobre os fatores de risco específicos desta população e aprimorar as estratégias terapêuticas.

Dessa forma, este estudo reforça a necessidade da monitorização regular dos cães predispostos à cardiomiopatia dilatada, bem como a adoção de protocolos diagnósticos como a ecocardiografia e o exame Holter para auxiliar no diagnóstico da doença. O aprimoramento das diretrizes terapêuticas pode levar a um melhor controlo da doença e à melhoria da qualidade de vida dos animais acometidos. Assim, torna-se essencial a continuidade das pesquisas nesta área, visando avanços no entendimento da doença e na sua abordagem clínica.

Palavras-chave: Cão/ Cardiomiopatia Dilatada/ Disfunção sisólica/ Insuficiência cardiaca congestiva

Abbreviations, acronyms and symbols

ACE: Angiotensin-converting enzyme

ACVIM: American College of Veterinary Internal Medicine

AF: Atrial fibrillation

AHA: American Heart Association

AI: Aortic insufficiency

ANP: Atrial natriuretic peptide

Ao: Aorta diameter

Apeak: Peak velocity of the A wave

ARVC: Arrhythmogenic right ventricular cardiomyopathy

AVB: Atrial ventricular block

AVpeak: Peak blood flow at the level of the aorta

AVpeakPG: Peak aortic pressure gradient

AWF: Attenuated wavy fiber type

BSA: Body surface area

CBM: Cardiac biomarkers

CHF: Congestive heart failure

cTNI: Cardiac troponin I

DCM: Dilated cardiomyopathy

ECG: Electrocardiography

EDV-I: End-diastolic volume index

EF: Ejection fraction

Epeak: Peak velocity of the E wave

EPSS: Peak of the E wave and the interventricular septum

ESV-I: End-systolic volume index

EWDT: E wave deceleration time

FDA: Food and Drug Administration

FID: Fatty infiltration-degenerative type

FS: Fractional shortening

GSD: German shephard dogs

GWAS: Genome-wide association studies

HR: Heart rate

ISACHC: International Small Animal Cardiac Health Council

IVSd: Interventricular septal thickness at end-diastole

IVSs: Interventricular septal thickness at end-systole

LA: Left atrium diameter

LBBB: Left bundle branch block

LV: Left-ventricle

LVAd: Area of the left ventricle at end-diastole

LVAs: Area of the left ventricle at end-systole

LVEDV: Left ventricular volume at end-diastole

LVEF: Left ventricular ejection fraction

LVESV: Left ventricular volume at end-systole

LVET: Ejection time in the left ventricle

LVEV: Left ventricular ejection volume

LVIDd: Left ventricular internal dimension at end-diastole

LVIDs: Left ventricular internal dimension at end-systole

LVLd: Left ventricle length at end-diastole

LVLs: Left ventricle length at end-systole

LVPWd: Left ventricular posterior wall thickness at end-diastole

LVPWs: Left ventricular posterior wall thickness at end-systole

MI: Mitral insufficiency

NSB: Non-specific breed

NT-proBNP: N-terminal pro-B-type natriuretic peptide

NYHA: New York Heart Association

PDK4: Pyruvate dehydrogenase kinase 4

PEP: Pre-ejection period

PH: Pulmonary hypertension

PI: Pulmonary insufficiency

PLN: Phospholamban gene

PVpeak: Peak blood flow of the pulmonary valve

PVpeakPG: Peak pulmonary pressure gradient

RAAS: Renin-angiotensin-aldosterone system

RMVpeak: Mitral regurgitation peak velocity

RMVpeakPG: Mitral regurgitation peak gradient

RTVpeak: Tricuspid regurgitation peak velocity

RTVpeakPG: Tricuspid regurgitation peak

SA: Sinus arrhythmia

SAR: Sinus arrest

SCD: Sudden cardiac death

SI: Sphericity index

SNPs: Single nucleotide polymorphisms

SPCs: Supraventricular premature complexes

SR: Sinus rhythm

ST: Sinus tachycardia

STRN: Striatin gene

SVT: Supraventricular tachycardia

T3: Thyroid hormone triiodothyronine

TI: Tricuspid insufficiency

TMF: Transmitral flow

TTN: Titin gene

USA: United States of America

VEB: Ventricular escape beat

VPCs: Ventricular premature complexes

VT: Ventricular tachycardia

WHO: World Health Organization

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Internship at Hospital Veterinário do Porto

The author completed the internship at Hospital Veterinário do Porto from September 2023 until March 2024, corresponding to a period of 6 months. The author was present in 467 clinical cases of different specialties and 64 surgeries (Figure 1). From the 467 clinical cases observed, 110 belonged to cardiology, 78 corresponded to the urology system, 69 from the digestive system, 44 from oncology, 30 from dermatology, 27 from infectiology, 27 from endocrinology, 25 from the respiratory system, 20 from neurology, 13 from the musculoskeletal system, 10 from theriogenology, 9 from ophthalmology, 3 hematology and 2 toxicology (Figure 2). According to the 64 surgeries, 49 were soft tissue surgeries, 7 were minimal invasive surgeries, 5 were orthopedic and 3 were ophthalmologic (Figure 3).

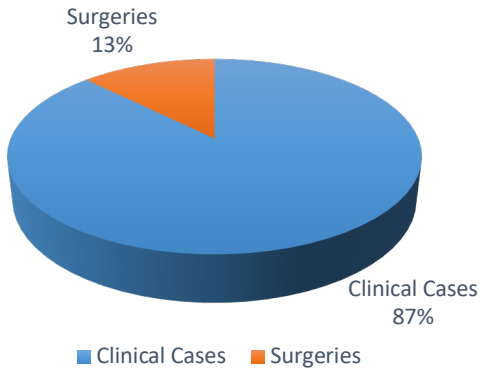


Figure 1 – Distribution of the casuistry done at Hospital Veterinário do Porto

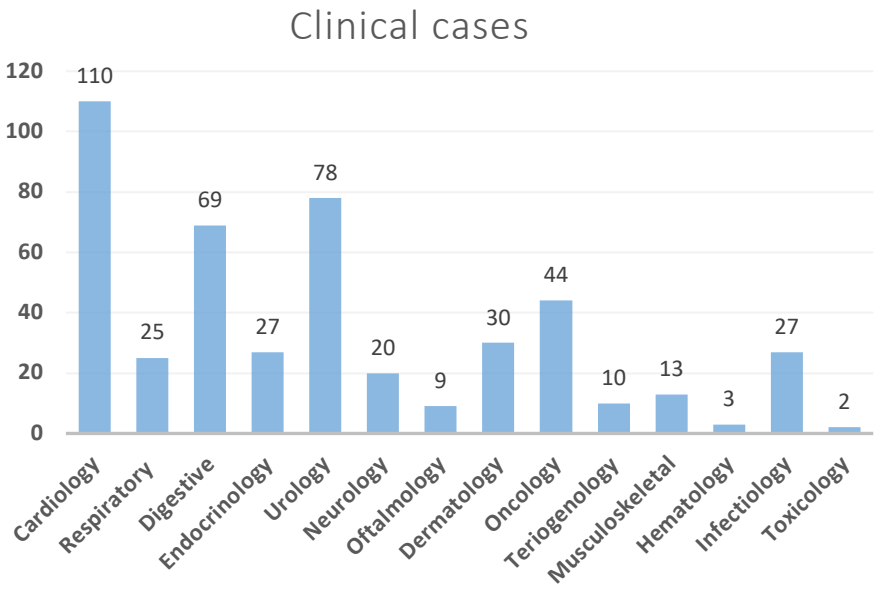


Figure 2 – Number of clinical cases observed on each specialties

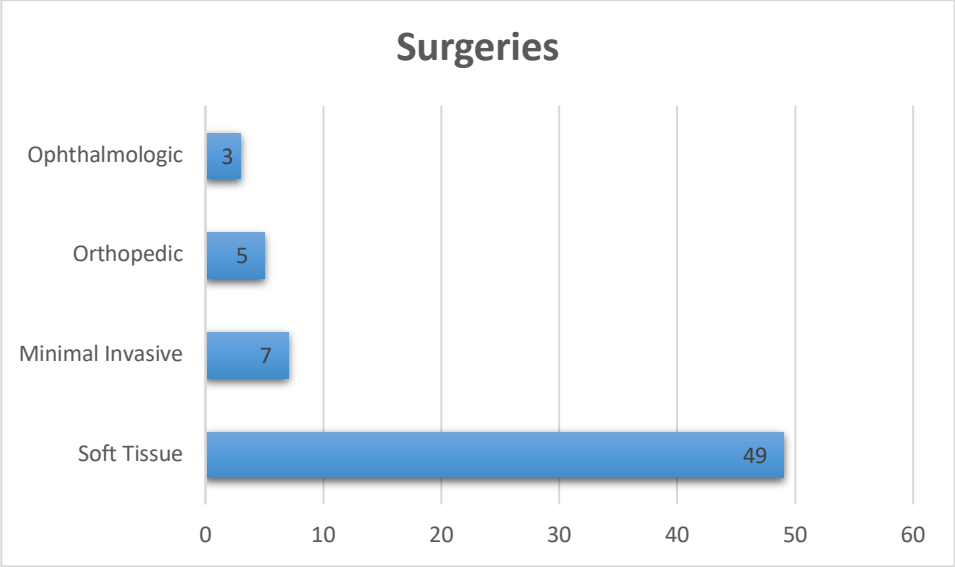


Figure 3 – Distribution of the surgeries observed at Hospital Veterinário do Porto

1. Introduction

1.1. Definition

DCM belongs to a group of cardiomyopathies characterized by mechanical or electrical dysfunction of the myocardium (Wess et al., 2017a). In 1980, the World Health Organization (WHO) identified three major groups of cardiomyopathies: dilated, hypertrophic, and restrictive ("Cardiomyopathies. Report of a WHO Expert Committee.," 1984). However, in 2006, the American Heart Association (AHA) introduced a new classification system for cardiomyopathies in human medicine. Advances in diagnostic techniques and a deeper understanding of various cardiomyopathies rendered the WHO classification outdated, necessitating a revised framework (Maron et al., 2006).

The rapid evolution of molecular genetics in cardiology, along with the recognition of ionic channelopathies, led to the reclassification of cardiomyopathies into two broad categories: primary cardiomyopathies and secondary cardiomyopathies (Maron et al., 2006).

On one hand, primary cardiomyopathies are the ones where, only or predominantly, the myocardium is affected. This major group is now categorized into three groups: genetic, acquired, and mixed. As a result, DCM falls under the primary mixed category (Maron et al., 2006). On the other hand, secondary cardiomyopathies refer to heart muscle involvement that occurs as part of various systemic disorders. These diseases have previously been labeled as "specific cardiomyopathies" or "specific heart muscle diseases" in older classifications, but those terms are no longer used. The extent and frequency of heart muscle involvement can vary significantly among these disorders, with some being quite rare and with limited evidence of heart pathology reported in only a few patients. Since many cardiomyopathies primarily affect the heart but may also impact other organs, the line between primary and secondary cardiomyopathy is somewhat subjective and depends on clinical judgment regarding the importance and consequences of heart-related issues (Maron et al., 2006).

In 2014, a new classification called MOGES was proposed by the World Heart Federation. This system was made to provide a more comprehensive description of the clinical phenotype and pathophysiology of cardiomyopathies (P. Elliott, 2023). The first subject (M) consists of the morphological and functional phenotype of the disease. The term (O) evaluates if there is an organ involvement, introducing details about manifestations of diseases outside of the heart. The third aspect (G) involves documenting family history and constructing a multi-generational

family tree to identify potential genetic patterns or predispositions. The fourth domain (E) refers to aetiology and encompasses information related to genetic factors, infections, or inflammatory processes that may contribute to the condition. Finally, the term (S) indicates the stage of the disease (P. Elliott, 2023).

DCM is the most prevalent cardiomyopathy in dogs and the second most common heart disease among the canine population (Lobo, 2011). The disease is characterized by a slow and progressive systolic dysfunction, evolving to the dilation of the heart chambers (TIDHOLM et al., 2001). There are three different stages of the disease. The first stage matches a genetic predisposition being that the heart is morphologically and electrically normal. In the second stage, or occult phase, there is no evidence of clinical signs but abnormalities of the myocardium or electrical function of the heart are present. At last, in the third stage, or clinical phase, signs of congestive heart failure (CHF) are present (Bussadori, 2023).

According to the European Society of Veterinary Cardiology screening guidelines for DCM in the Doberman Pinscher, the occult stage can be present for many years before clinical signs appear. The morphologic alterations consist of the left ventricular enlargement in systole first, and then it happens in diastole. The electrical function of the heart can also be compromised, with ventricular premature complexes (VPCs) being a common finding in Dobermans. Furthermore, sudden death as a consequence of ventricular tachycardia and fibrillation is estimated to occur in the occult stage at least in 25% to 30% of dogs with DCM. Whether the disease is caused by a morphologic or electrical dysfunction, both can coexist, or one of them can be more present (Wess et al., 2017b).

1.2. Aetiology

Over the years, several factors, such as nutritional deficiencies, family history and genetic factors, metabolic disorders, infectious diseases, toxins or drugs, tachycardia, and the immunologic system, have been considered possible triggers for the development of DCM (TIDHOLM et al., 2001). In most cases, a specific aetiology cannot be classified, so it ends up being idiopathic (Lobo, 2011).

1.2.1. Nutritional

Studies have revealed that dogs with protein-restricted diets are more likely to show low levels of taurine, therefore they can easier develop secondary DCM (Lobo, 2011). Also, diets

restricted in carnitine and taurine have been shown to generate myocardial hypokinesis in humans, dogs, and cats (TIDHOLM et al., 2001). For this reason, many diets are now supplemented with taurine (Lobo, 2011). Some breeds are more likely to present this deficiency, like American Cocker Spaniel, Golden Retriever, and Newfoundland, but other giant breeds are also predisposed. It has been shown that the myocardio benefits when the dog is supplemented with taurine diets. The United States Food and Drug Administration (FDA) performed two studies to discover a possible correlation between diet and DCM. In one of the studies, they evaluated Golden Retrievers diagnosed with DCM, and all of them had low circulation of taurine concentrations. In the other study, more than 15 different breeds of dogs were diagnosed with DCM that could be diet-associated. What remained uniform across the studies, though, is that the majority of dogs had been provided with grain-free diets, and a significant number of the dogs who underwent follow-up examinations displayed clinical and echocardiographic enhancements when the diet was changed. However, it is still necessary to collect more information regarding this topic to establish a relationship between DCM and nutritional deficiencies (Freid et al., 2021).

1.2.2. Genetics

In humans, in 20% to 48% of the patients, DCM is believed to be familial (Lobo, 2011;Meurs et al., 2007) In dogs, DCM tends to manifest more prominently within certain breeds or familial groups, suggesting a hereditary component (Lobo, 2011;Meurs, 1998). Different breeds with DCM may present distinct clinical signs and survival times. Therefore, multiple patterns of inheritance have been proven: autosomal dominant, autosomal recessive, X-linked (dominant and recessive) and mitochondrial (Meurs, 1998;Meurs et al., 2007;Wiersma et al., 2007). It is believed, that some groups of genes have a major role in the development of DCM (Meurs, 1998). One of the groups includes genes that encode cytoskeletal proteins which provide structural support for the myocytes, but also allow them to resist mechanical stress (Meurs et al., 2007). In this group, the dystrophin gene is an example of X-linked DCM and when it suffers a mutation, induces the death of cardiac myocytes (Meurs, 1998;TIDHOLM et al., 2001). In addition, other genes like ACTC are located on the autosomal chromosomes. On top of that, some dogs present arrhythmias, which can be associated with mutations in genes encoding sodium and potassium channels. (Wiersma et al., 2007). Although, a specific genetic mutation is not identified often in a big part of time, alterations in 24 genes have been shown in humans (Meurs et al., 2007). Two methods are used to correlate genes with canine DCM: candidate gene studies and, more recently, genome-wide association studies

(GWAS) (Simpson et al., 2015). With different loci being recognized, most of them on different chromosomes, DCM in dogs is revealed to be a complex subject (Gaar-Humphreys et al., 2022).

In Dobermanns, two mutations in diverse genes are associated with DCM. One of them consists of a 16-base pair deletion at the donor splice site of an intron 10 in the pyruvate dehydrogenase kinase 4 (PDK4) gene and this mutation is transmitted by an autosomal dominant pattern with 60-68% penetrance (Gaar-Humphreys et al., 2022). A genetic test based on the 16-bp deletion in the PDK4 gene was made and despite being useful in the USA, a different study revealed no association between PDK4 and DCM in Europe (Wess et al., 2017b). The other identified mutation correlated with DCM, is a single variation in the titin (TTN) gene where the amino acid glycine is changed to arginine. This gene plays a crucial role in heart muscle contraction by undergoing unfolding and folding processes in response to tension, and it serves as the connection between myosin and the Z-discs of sarcomeres, being the largest protein in the body. This mutation has a prevalence of up to 58% in Dobermanns and both PDK4 and TTN alterations have already been observed in a single dog with DCM (Gaar-Humphreys et al., 2022). If Dobermanns do not present a genetic mutation linked with DCM, that doesn´t ensure the dog will never develop DCM. Furthermore, if a genetic mutation is identified, that should not be considered a death sentence, and the dog may not manifest the disease in the future. In this case, a follow-up and screening for DCM is advised (Wess et al., 2017b).

An autosomal inheritance pattern for a familial form of DCM was proposed in the Irish Wolfhounds and the Newfoundlands (TIDHOLM et al., 2001). However, in another study, it was not possible to identify a chromosomal region that could be linked with DCM in the Newfoundlands (Meurs et al., 2007). In Irish Wolfhounds, since the prevalence of the disease is significantly higher in males than in females, X chromosome markers were evaluated for association with DCM, as well as a human X chromosome candidate gene (Lobo, 2011). The prevalence of DCM in this breed has shown to be between 24% and 29%. A group of single nucleotide polymorphisms (SNPs), which are associated with the development of DCM, have been discovered on six different chromosomes, and three of them are found in known genes: ARHGAP8, FSTL5 and PDE3B. The SNP on chromosome 37 can be found between the MOGATI and the ACSL genes, while the SNPs situated on chromosomes 1 and 17 are between introns (Gaar-Humphreys et al., 2022). Also, a genome-wide linkage study in Portuguese Water Dogs was performed to evaluate which locus of the autosomal recessive inheritance pattern

causes this juvenile form of DCM in this breed. The study showed that a locus on canine chromosome 8 correlated with the disease was identified (Werner et al., 2008;Gaar-Humphreys et al., 2022). A GWAS in Boxers uncovered a mutation in the striatin gene (STRN), responsible for a form of adult-onset cardiomyopathy called "boxer cardiomyopathy." In a pedigree scanning, the mutation was revealed to be both homozygous and heterozygous. The homozygous variation showed significantly more arrhythmias and clinical signs were observed at an earlier age. All boxers diagnosed with DCM didn´t necessarily have the STRN mutation, so other mutations yet to be found can cause the disease in this breed (Gaar-Humphreys et al., 2022). In the Welsh Springer Spaniels, a mutation in the phospholamban (PLN) gene was discovered and linked to a notable incidence of left ventricular dilation, arrhythmia and premature sudden cardiac death. A study showed the penetrance of this mutation was very high in this breed since all dogs with this transfiguration developed a phenotype. The same mutation was proven to exist in humans but with a significantly lower penetrance (Gaar-Humphreys et al., 2022). In a study with Great Dane dogs, based on their myocardial tissue, researchers tried to determine which genes can be expressed differently as a way of identifying candidate genes for future studies (Lobo, 2011). In the future, a better knowledge of genes that can lead to DCM will enable selective breeding strategies with the purpose of reducing the number of affected animals with DCM, promoting, in this way, the long-term well-being of the breed. Despite that, advances in the diagnosis, treatment and prognosis of this condition may also be improved. Finally, novel mutations in dogs could play a role as candidate genes in humans with DCM, which can bring great benefits to human medicine (Simpson et al., 2015).

1.2.3. Metabolic

Of the metabolic disorders, diabetes mellitus, pheochromocytoma and hypothyroidism were associated with DCM (TIDHOLM et al., 2001).

The thyroid hormone triiodothyronine (T3) is known to control genes that produce proteins crucial for heart muscle function, such as Na, K-ATPase, Ca-ATPase, β-adrenergic receptors and myosin heavy chains. Experimental studies on dogs reveal that the strength of contraction of the left ventricle directly correlates with the thyroid condition (R. R. Taylor et al., 1969). So, when a deficiency in the T3 hormone occurs, there is a diminished left ventricular systolic function, low QRS voltages, inverted T waves, weak apex beat and sinus bradycardia (Panciera, 1994;Panciera,2001;Scott-Moncrieff,2012). For this reason, the possibility that hypothyroidism can lead to DCM has been discussed (Beier et al., 2015). However, a casual relationship

between hypothyroidism and DCM has not been documented in recent literature (Flood & Hoover, 2009).

Even so, the euthyroid sick syndrome, a condition whereby some nonthyroidal disease leads to suppression in serum concentrations of circulating thyroid hormone, has been associated with cardiac illness, especially in Doberman Pinchers (Beier et al., 2015). TT4 lowered, and to some extent, fT4, in euthyroid sick syndrome can be misleading and may lead to an incorrect diagnosis of hypothyroidism. Thyroid ultrasound represents a reliable method that allows one to make a differential diagnosis of hypothyroid versus euthyroid sick dogs (Beier et al., 2015).

In a study performed with two Great Danes, both diagnosed with DCM and primary hypothyroidism, the administration of levothyroxine showed to be promising, since the dogs presented better myocardial contractility with a higher fractional shortening and a decrease in left atrial size and also in left ventricular end-systolic and diastolic diameters. Furthermore, all the cardiac improvements with levothyroxine supplementation remain, even with the discontinuation of cardiac common drugs like digoxin and IECA´s (Phillips & Harkin, 2003). These findings imply that hypothyroidism may lead to DCM in Great Danes, which can be partially or entirely reversed with thyroid hormone replacement therapy. Therefore, hypothyroidism should be taken into account in all Great Danes showing signs of systolic dysfunction. However, since a direct cause and effect between hypothyroidism and cardiomyopathy has not been clarified, it is possible that these conditions were concomitants (Phillips & Harkin, 2003). On the other hand, a few studies performed in the Doberman Pinscher refused the possibility of hypothyroidism being considered as an aetiology of DCM in this breed (Calvert et al., 1982;Calvert et al., 1998). It has also been documented that no relevant differences in cardiac size and other cardiac variables were found between hypothyroid dogs and non-hypothyroid dogs, even after being treated with levothyroxine (Beier et al., 2015).

Studies in humans but also animal models have shown that CHF, in severe DCM, leads to a turn in myocardial metabolic substrate consumption from free fatty acids to glucose (M. Taylor et al., 2001;Dávila-Román et al., 2002). Consequently, there is a reduction in fatty acid metabolism and a rise in the uptake of glucose (Dávila-Román et al., 2002). This phenomenon can be explained because fatty acid oxidation consumes more oxygen per unit of work than glucose, so the myocardium becomes more energetically efficient with this last route (M. Taylor et al., 2001). In another study, has been demonstrated that left ventricle dysfunction was

occurring simultaneously with myocardial insulin resistance, in dogs affected with DCM in an advanced stage. (Nikolaidis, 2004).

1.2.4. Infectious and Immunological

In human medicine, infectious and immunological aetiology has been proven to be a leading cause of DCM (Buse et al., 2008;Pankuweit et al., 2009). Some of the most common agents associated with human inflammatory DCM range from viruses, such as enteroviruses and adenoviruses, to bacteria, to protozoa, like *Toxoplasma gondii* and *Trypanosoma cruzi*, or even fungi (Pankuweit et al., 2009). In veterinary medicine, it has been demonstrated the possibility that some viruses like parvovirus, adenovirus, herpes virus and distemper virus, may cause myocarditis or chronic myocardial lesions with fibrosis, cardiomegaly and CHF (Maxson et al., 2001). However, scientific data doesn´t support this aetiology as a cause of DCM (Maxson et al., 2001). In a study performed with juvenile Doberman Pinchers, a parvoviral infection tested negative for PCR, but other viral infections could not have been excluded from leading to myocardial disease (A. Vollmar et al., 2003). Another study in this breed showed the absence of parvoviral DNA in myocardium samples (Braz-Ruivo, 1999). Furthermore, other research identified an anti-herpes virus agent named vidarabine which avoids myocardial apoptosis and fibrosis, not only in the left ventricle but also in the atrium (Nakamura et al., 2016).

Autoantibodies have been detected targeting mitochondria(Klein et al., 1984), the mitochondrial ADP/ATP transporter (SCHULTHEISS & BOLTE, 1985;Schulze et al., 1990), cardiac β-adrenergic receptors (Limas et al., 1989;Limas, 1996) and myosin heavy chains (α and β) (Caforio et al., 1992). Another study performed in a colony of English Cocker Spaniels, anti-mitochondrial antibodies were identified in 30% of the dogs (Day, 1996). However, the autoantibodies are not necessarily linked with DCM and they can act in other cardiac diseases as well as myocarditis, hypertrophic cardiomyopathy and systemic hypertension (Autore et al., 1988). On the other hand, a review could not show the presence of anti-myocardial antibodies in dogs with DCM (Cobb et al., 1994). Nevertheless, the possibility of immunologic responses against myocardial proteins including contractile, regulatory or cytoskeletal matrix proteins, as well as extracellular matrix or membrane proteins can not be ruled out (O'Grady & O'Sullivan, 2004). Despite the immunologic processes associated with DCM pathogenesis, a cause-efect relationship needs further investigation (TIDHOLM et al., 2001).

1.2.5. Drugs and toxins

Doxorubicin is an anthracycline antitumor antibiotic which promotes cardiotoxicity, when administered several times in humans and dogs (Hallman et al., 2019). This drug leads to arrhythmias and impaired systolic function and, consequently, to a condition similar to DCM (Hallman et al., 2019). However, a report published recently demonstrated no relevant cardiotoxicity under echocardiogram and electrocardiogram in dogs, without predisposing factors to DCM, submitted to four doses of doxorubicin, in a 30-minute infusion protocol (Tang & Wang, 2024). Other anti-neoplastic agents like ethanol, cobalt, lead, catecholamines, histamine, methylxanthines, and vitamin D may develop cardiomyopathies and damage to the myocardium in different ways (Van Vleet & Ferrans, 1986). Vacuolization of myocytes and necrosis is commonly seen in the presence of doxorubicin, but also fatty infiltration is often identified in cardiomyopathies caused by ethanol (DAVIES, 1984).

1.2.6. Persistent tachycardia

The heart rate has a major impact on the left ventricular systolic function and many reports, with experimentally induced tachycardia, show that heart rates higher than 240 beats per minute under 3 or 4 weeks lead to CHF, chamber dilatation and reversible hypokinesis in dogs (Armstrong et al., 1986;O'Brien et al., 1990;O'Brien et al., 1993). Tachycardia-induced myocardial failure is associated with higher oxygen consumption, increased capillary-myocyte distance (Spinale et al., 1992), myocyte cell loss (Mahmoudabady et al., 2013), their elongation and hypertrophy (Kajstura et al., 1995;Jovanovic et al., 1999), reduced production of cAMP, abnormal calcium handling (Perreault et al., 1992) and changes in left ventricular norepinephrine concentrations and sarcoplasmic reticular and myofibrillar CaATP-ase. These mechanisms turn out to be similar to those that occur when there is an increase in heart volume and an increase in blood pressure (O'Brien et al., 1990). In dogs with DCM, tachyarrhythmia can be a consequence or, in many cases, a cause of DCM (Wright, 2000) leading to a tachycardiomyopathy (Menaut et al., 2005). In other recent reports, tachycardia-induced DCM in canine models, showed significant LV intraventricular dyssynchrony (Salimian et al., 2017) and also a decrease in the LV systolic pressure (Kusunose et al., 2013).

1.3. Demography

1.3.1 Breed

DCM is one of the most frequent cardiomyopathies among dogs, affecting a significant portion of the canine population, with estimated prevalence rates between 0.5% and 1.4%. This

condition tends to be more frequently seen in large and giant breeds, with a particularly high incidence in Dobermans, Great Danes, Newfoundlands and Irish Wolfhounds. However, it is not limited to these breeds and can also be seen in smaller and medium-sized dogs, such as Portuguese Water Dogs, Cocker Spaniels and Schnauzers (Bussadori, 2023). However, some breeds are overrepresented in some countries because of the canine population in those regions(D. Sisson et al., 1999). For example, in The United States of America (USA) the breed more affected is without a doubt the Doberman Pincher, in Sweden is the Newfoundland, in Italy is the Great Dane and in Portugal, one in four dogs with DCM is Estrela Mountain (Monnet et al., 1995;Tidholm & Jonsson, 1997;Luís & Carvalho, 1998;Borgarelli et al., 2006;Martin et al., 2009). Despite being possible to diagnose DCM in mixed breed dogs, its prevalence is very low, being around 0,8 and 1,6 %(Lobo, 2011). In a retrospective study carried out in 2021 in the USA, they studied the prevalence of DCM in 71 dogs and 18 different breeds. The study showed that the breeds more affected were Doberman Pincher, Great Dane, Boxer, Golden Retriever, Labrador Retriever and French Bulldog, respectively (Freid et al., 2021). In England, another study was performed to know better the incidence of the disease in this country. They studied 369 dogs and only 4 weren´t pure breed dogs. The study encompassed 35 different breeds and the most common observed were Dobermanns (59), Boxers (53), Great Danes (38), Cocker Spaniels (30), German Shephard (24), Saint Bernards (20) and Labradors (20). Nevertheless, other breeds were also present as Irish Wolfhound (17), Golden Retriever (15), Newfoundland (14) and Old English sheepdog (9) (Martin et al., 2009).

1.3.2 Sex

During the last few years, research has proven that DCM is mainly frequent in males, but the incidence in females is getting bigger (Lobo, 2011). According to a study carried out by Martin et al. (2009), 73% of the dogs with DCM were male and 27% were female, having a ratio of 2.7:1 (male:female). Even so, some breeds have a bigger discrepancy in this subject than others. The study demonstrated that Great Danes and German Shephard dogs, when diagnosed with DCM, are very more likely to be males, having a ratio of 6:1. On the other hand, dogs like Dobemann and Saint Bernard showed a ratio of 5:1 and Boxers, Golden Retrievers, Cocker Spaniels and Labradors had, more or less, 3:1 ratios.

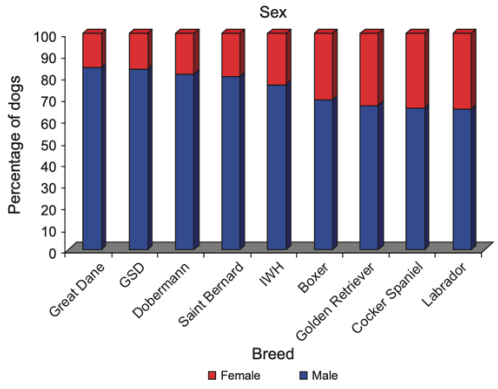


Figure 4 – Ratio of male compared with female dogs according to different breeds (Martin et al., 2009)

More research has demonstrated an equal distribution of the disease between males and females in Europe (Wess et al., 2010). The variation in gender ratios reported in earlier and later studies may be explained by the inclusion of a Holter or ECG exam as part of diagnosis procedures. In general, it is observed that male Dobermans present morphological changes earlier than females, which can be visible by doing an echocardiogram. As so, males are more likely to develop DCM at a younger age and also have a shorter life expectancy. In females, the progression of the disease seems to not be that fast, with the detection of VPCs as the only anomaly in some cases, even at an older age. However, most female Dobermans will eventually have the typical cardiac morphological changes associated with DCM, although usually at an older age than males (Wess et al., 2017b).

1.3.3 Age

The occult phase of DCM typically gets identified in dogs aged between 5 and 7 years, although it can be seen in younger dogs (Bussadori, 2023). A juvenile variant of DCM has been identified in Portuguese Water Dogs, where puppies usually succumb before reaching 7 months of age (Bussadori, 2023). Despite that, DCM can occur at any age from 4 years until 10 years of age, where clinical signs such as CHF are many times present. Besides that, older dogs have a higher risk of being affected and the onset of clinical signs in young dogs is an indicator of poor prognosis (Lobo, 2011). According to the European Society of Veterinary Cardiology screening guidelines for DCM in Doberman Pinchers, echocardiography and Holter exam should be performed at 3 years of age and this should be done at least once each year. Screening DCM at a young age is crucial to decrease the breeding population of affected Dobemanns and to assure an efficient treatment of the disease, leading to a higher life expectancy and reduction of the prevalence of DCM in future generations (Wess et al., 2017b).

1.4. Pathology and Pathophysiology

Pathology

The hearts of dogs that have died from DCM typically show an increased size and enlarged chambers. This dilation may involve all four chambers of the heart or primarily the left side. The combination of an increased heart weight/body weight ratio and chamber dilation usually indicates eccentric hypertrophy (Bussadori, 2023). Also, a diminished ratio of left ventricular wall thickness to chamber diameter is a relevant finding (TIDHOLM et al., 2001).

Despite these pathological findings being common in dogs with DCM, they are not pathognomonic from the disease (Bussadori, 2023). The morphology of atrioventricular valves starts to change, as a consequence of ventricular dilation, resulting in valvular abnormalities (Janus et al., 2016). When mitral regurgitation gets higher, the pressure in the left atrium grows which contributes to the remodelling of the left chambers (Janus et al., 2016).

The major histopathological alterations in the heart muscle consist of fibrosis, degeneration and attenuation of myocardial fibres, described as wavy fibres, vacuolization of the cytoplasm, fatty accumulation, myocyte hypertrophy, fibre diameter variability of the myocardium and necrosis, less frequent. In severe cases, these abnormalities are typically more noticeable at the base of the papillary muscles and in the subendocardial region of the left ventricular free wall (TIDHOLM et al., 2001;Bussadori, 2023). These lesions can also be observed, less common, in the myocardium of the right ventricle and the interventricular septum (Bussadori, 2023).

Based on recent literature, two forms of histopathologic findings in the ventricular myocardium have been written, according to the breed of the affected dog: the attenuated wavy fibre type (AWF) and the fatty infiltration-degenerative type (FID) (Janus et al., 2016;Gasparini et al., 2020). The AWF type presents myofiber atrophy and a large wavy look of fibres and is more prevalent in giant breeds, although it can also appear in Boxers and Doberman Pinschers. The FID type is characterized by the destruction of the myofibers, fibrosis and lipid accumulation, being mainly reported in Bullmastiffs, Boxers and Dobermanns (TIDHOLM et al., 2001;Gasparini et al., 2020). In contrast, Great Danes showed to present either FID or AWF and both simultaneously (Gasparini et al., 2020). Also, in the Newfoundlands with a known susceptibility for DCM, but without any clinical or echocardiographic signs of the pathology, the AWF type was detected in the myocardium (TIDHOLM et al., 2001). Arrhythmogenic right ventricular cardiomyopathy (ARVC) in Boxers is characterized by substantial fibrosis, myocytolysis, degeneration of the myocytes and also fatty infiltration and vacuolization of the

myocardium cells, just like the FID type of DCM in the Dobermanns Pinchers (TIDHOLM et al., 2001;Janus et al., 2016;Bussadori, 2023). Based on these findings, some authors now believe a form of ARVC can be present in the left ventricle of Dobermanns with DCM (Bussadori, 2023).

According to recent studies, it has been proven that these pathological results are different for each breed, having a different cardiomyocyte response to the disease or dissimilar pathogenesis (Gasparini et al., 2020). Having said that, the AWF type is the most seen histologic finding with a prevalence of up to 100% in some reports. Because of this, the presence of AWF is evaluated, by some authors, to be pathognomonic for canine DCM (Bussadori, 2023).

Nonetheless, the atrophy of cardiomyocytes might also indicate the cells' reaction to a bad contraction activity or to pathological triggers. Muscle fibre wasting often occurs in response to conditions that inhibit normal contraction. On the other side, myocyte hypertrophy was noted in seven studies on human DCM, with five of these studies also reporting simultaneous myocyte shrinkage. Consequently, it remains uncertain whether the presence of reduced wavy fibres is a distinctive feature of DCM, or if it is a nonspecific finding resulting from various pathological processes (TIDHOLM et al., 2001;Bussadori, 2023).

As a result, remodelling processes and focal lesions are often seen in the cardiac muscle of dogs diagnosed with DCM and not only cardiomyocytes but also macrophages, are involved in this pathology through the generation of cytokines, adhesion molecules and enzymes which, at some point, have a leading path to cardiac dilation and dysfunction (Gasparini et al., 2020).

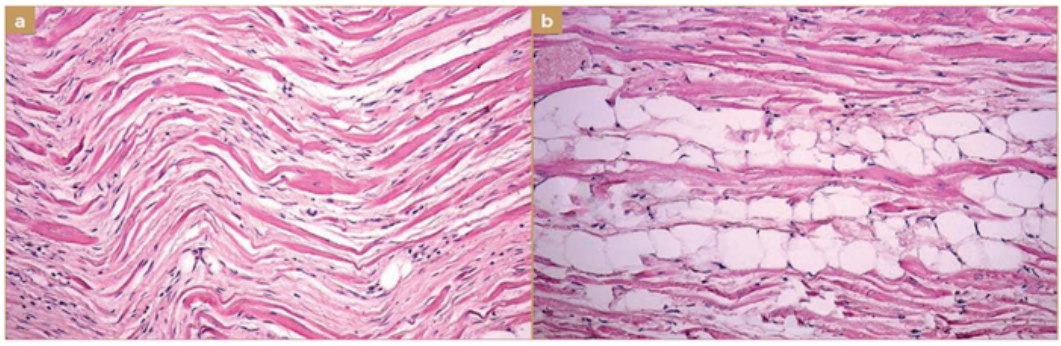


Figure 5 – Characterization of histological samples from the left ventricle

a) Histopathological samples of the AWF type taken from the left ventricle. b) Histopathological samples of the FID type taken from the left ventricle (Bussadori, 2023).

Pathophysiology

A systolic dysfunction is the trigger to develop DCM, leading to a low cardiac output (Bussadori, 2023). This can be flagged by the baroreceptors in the aortic arch and carotid sinus (McEwan, 2000). Consequently, a neurohormonal response is activated, involving the sympathetic nervous system, the renin-angiotensin-aldosterone system (RAAS) and vasoactive peptides. Ultimately, these factors will contribute to compensatory eccentric hypertrophy and CHF can occur at a more advanced stage (Borgarelli et al., 2001;Bussadori, 2023)

The sympathetic nervous system gets activated, as a compensatory system, with an increase in heart rate and contractility, along with peripheral vasoconstriction and central vasodilation (J. Elliott & Marr, 2001;Bussadori, 2023). Due to the tachycardia, the oxygen demand from the myocytes is higher, as the capillary-myocyte distance, which results in the elongation and hypertrophy of the myocytes (TIDHOLM et al., 2001). A prolonged stimulation of sympathetic tone can have very bad effects like the decrease of β1-adrenergic receptors in their number, density, and activity which reduces the responsiveness to catecholamines (Bussadori, 2023). Catecholamines directly harm cardiac myocytes by causing hypertrophy and apoptosis. They can also intensify arrhythmias, produce myocardial ischemia, and lead to multi-organ failure due to regional vasoconstriction. Elevated levels of norepinephrine in circulation and downregulation of β1-adrenergic receptors have been observed in both preclinical and clinical cases of DCM in dogs (Bussadori, 2023). While this downregulation initially protects the myocardium, it eventually leads to energy deprivation, worsening systolic function over time (Bussadori, 2023). Deficient production of ATP within the mitochondria has been reported in Doberman Pinschers, like reduction of NADH dehydrogenase and lowering of ATP synthetase. However, a decrease in myoglobin concentrations has also been documented (TIDHOLM et al., 2001)

The RAAS mechanism is activated with a deficient renal perfusion and the stimulation of β1-adrenergic receptors, at the level of the juxta-glomerular apparatus, leading to renin release. This substance will have an impact on the angiotensinogen, which is produced in the liver, forming another molecule called angiotensin I. Afterwards, angiotensin I is converted into angiotensin II and this last substance is catalysed by angiotensin-converting enzyme (ACE). Finally, angiotensin II will increase the levels of aldosterone and, thereafter, the retention of sodium and water is higher (McEwan, 2000). The RAAS is a system that operates to normalize arterial pressure by enlarging plasma volume (sodium and water retention), arteriolar

vasoconstriction, growing afterload, and promoting thirst (Borgarelli et al., 2001). The water and sodium retention results in edemas and effusions that contribute to CHF and the acceleration rate of myocardial cell death (McEwan, 2000;Borgarelli et al., 2001).

Atrial natriuretic peptide (ANP) reduces renin and aldosterone production, opposes the action of angiotensin II, decreases sympathetic nervous system activity, and inhibits vasopressin release. These actions work to compensate for the hormonal response of the body to cardiac dysfunction. The primary physiological effects of ANP are promoted natriuresis and thus a diuretic that allows greater production of urine, the widening of blood vessels (vasodilation) and decreased average arterial blood pressure. The main triggers for ANP release are atrial distension and tachycardia (Tidholm et al., 2001).

1.5. Diagnosis

To make a diagnosis of DCM, it is necessary to exclude other congenital, acquired and systemic comorbidities (Dukes-McEwan et al., 2003). It is also mandatory to identify LV dilation, reduced systolic function and higher sphericity of the heart (Dukes-McEwan et al., 2003). In veterinary practice, canine DCM only it´s going to be diagnosed when the dog develops clinical signs or other clinical abnormalities in the physical exam, excluding tracking programs for breeders (Martin et al., 2009;Lobo, 2011).

1.5.1 Anamnese

The best approach to a clinical case starts with the complete identification of the animal because characteristics such as breed, sex and age are relevant for the definitive diagnosis. In this case, DCM is a disease that covers a wide range of medium to large-sized dogs, mainly from pure breeds, with a higher risk in older dogs (Martin et al., 2009;Lobo, 2011). Afterwards, taking a deep look into the history of the patient is crucial, being that a few dogs could only have suffered a subtle and progressive exercise intolerance or weight loss (Lobo, 2011). Most dogs with DCM and congestive heart failure can present symptoms like breathlessness, cough, depression, exercise intolerance, inappetence, syncope, weight loss, abdominal distention and polydipsia (Dukes-McEwan et al., 2003). In a study with a large sample of dogs, breathlessness (67%) and cough (64%) were the most common symptoms, followed by exercise intolerance (48,8%), weakness (39,2%), reduced appetite (35,7%), weight loss (30,2%), collapse (26%) and lethargy (20%). Some symptoms were more evident in some breeds, for example, collapse

occurred most often in Boxers (70%) and inaptence was greater among Golden Retrievers (60%). The most common sign observed in Great Danes was weakness (55,3%) and exercise intolerance was most seen in GSD (61%) (Martin et al., 2009). It is believed, that the dogs that show symptomatology of DCM, only represent a small portion of all dogs affected by the disease, since the majority of affected dogs by DCM remain asymptomatic (Martin et al., 2009).

1.5.2 Clinical signs and Physical exam

Occult phase

In this stage, also called the "silent disease stage", the word ´occult´ is referred to the owner´s point of view. This means the dog looks apparently normal, despite echocardiographic or electrocardiographic findings (Wess, 2022). At this point, a systolic murmur over the left apex, an audible gallop sound on auscultation, a weak femoral pulse or pulsus alternans and an arrhythmia can be commonly detected in affected dogs (Sisson et al., 1999;Wess et al., 2017b;Bussadori, 2023).

Overt phase

The first clinical signs, associated with CHF and/or arrhythmias, appear in the overt phase, a more advanced stage of the disease, instead of the occult phase where there is a lack of clinical signs (Bussadori, 2023). The spectrum of clinical signs exhibited by dogs with DCM is very similar across all breeds, but the frequency of these signs may vary in the breeds that are more commonly affected (D. Sisson et al., 1999). In the juvenile forms of the disease, reported in Portuguese Water Dogs and Dobermans, this condition comes up very early in the dogs' lives, normally presenting a fulminant course after the appearance of clinical signs, especially in Portuguese Water Dogs (Sleeper et al., 2002;Vollmar et al., 2003).

At the physical exam, patients commonly present with dyspnea, tachypnea, rales, crackles, intense breath sounds, and tachycardia with or without arrhythmia. In some cases, there may be a systolic murmur of lower or medium intensity (grade I-III/VI). Other changes might include a more frequent third heart sound (S3), weak femoral pulses, pulse deficits along with pale mucous membranes, decreased body condition or even sporadically increased body temperature (Dukes-McEwan et al., 2003).

Left-sided congestive heart failure (CHF) in dogs is usually characterized by increased respiratory rate and effort, with thoracic auscultation often revealing louder bronchovesicular sounds or soft crackles. Ascites, hepatomegaly, and jugular venous distension are seen in dogs

with right-sided or biventricular CHF. Besides that, the presence of pleural effusion may be indicated by muffled heart sounds (Bussadori, 2023). In the study performed by Martin et al. (2009), the most prevalent signs were weak pulse (39%), murmur (33%), mucosal pallor (16%), ascites (15%) and a gallop sound (10%). Of the dogs with a murmur recorded, 56% were grade 1, 15% were grade 2, 24% were grade 3 and 5% were grade 4.

1.5.3 Complementary diagnostic exams

1.5.3.1 Radiography

While thoracic radiographs are relatively accessible for screening DCM, the absence of specific cut-off values to clearly define asymptomatic dogs with cardiac remodeling, severely limits their utility and is not also capable of diagnosing early systolic dysfunction (Wess, 2022). When the vertebral heart scale is normal, using breed-specific reference intervals in dogs with signs of CHF, the diagnosis of DCM is unconvincing. However, if a dog later presents with symptoms of CHF, radiographs can be beneficial for picturing changes from their clinical baseline (Wess, 2022).

Thoracic radiographs in dogs with clinical DCM usually reveal cardiomegaly, especially enlargement of the left atrium, venus congestion, and are also the gold standard for identifying pulmonary edema and pleural effusion (Dukes-McEwan et al., 2003;Bussadori, 2023). On the contrary, dogs that are still in the occult phase of DCM, normally present with left atrial or left ventricular enlargement findings (Dukes-McEwan et al., 2003). According to many reports, the most predominant clinical signs observed in thoracic radiographs were cardiomegaly and congestion (pulmonary edema or pleural effusion) (Baumwart et al., 2005;Martin et al., 2009;Harmon et al., 2017;C. Vollmar et al., 2019). As pulmonary edema gets worse, the presence of an interstitial and alveolar pattern begins to be visible (Bussadori, 2023).

In breeds such as Boxers and Dobermanns, cardiomegaly is not often evident and thoracic radiographs must be viewed carefully with left atrial dilation being the most frequently seen finding (Lobo, 2011;Bussadori, 2023). This can be explained due to the thoracic shape of this breeds (deep chests) and also because right or biventricular dilation is not so much common in this dogs (Lobo, 2011).

1.5.3.2 Eletrocardiography

In the majority of the cases, dogs with DCM present some irregularities on the ECG, like arrhythmias, abnormal amplitude or duration of P wave or alterations in the QRS complex, showing chamber dilation or conduction abnormalities (Dukes-McEwan et al., 2003).

Atrial fibrillation (AF) is the most common electrocardiographic anomaly detected in dogs with DCM (Borgarelli et al., 2001) and it can be observed on an in-house ECG since intermittent AF is rare (Wess, 2022). Multiple studies have identified a link between AF and DCM in Irish Wolfhounds, with lone AF often being suggested as an early indicator of potential DCM development (Brownlie & Cobb, 1999;A. Vollmar, 2000;C. Vollmar et al., 2019a).

Furthermore, VPCs and ventricular tachycardia are also common findings in breeds such as Boxers and Dobermanns (Dukes-McEwan et al., 2003) and can be present isolated or in the form of couplets, triplets or short intervals of ventricular tachycardia (Bussadori, 2023). This type of arrhythmia is more difficult to detect because this phenomenon is not very consistent throughout the day, leading to potential missed detections on an in-house ECG (Wess, 2022). It has been reported in Boxers, that there is a very high variability of VPCs daily, up to 85%. As a result, false negatives are often present and multiple Holter recordings are advised in this breed (Bussadori, 2023). A study performed on boxers revealed that 58% of the dogs diagnosed with DCM, showed a sinus rhythm with VPCs on the ECG (Baumwart et al., 2005). Besides, VPCs are also important to evaluate the risk of sudden cardiac death (SCD), which is believed to be caused by ventricular tachycardia (Wess, 2022). Ventricular arrhythmias such as VPCs can originate from other cardiac or systemic diseases, so they should be ruled out from the diagnose (Wess, 2022;Bussadori, 2023). On top of this, recent investigations have shown that atrial premature complexes are not an initial indicator of DCM in Dobermans. The relevance of this type of arrhythmia is yet to be found in other breeds (Wess, 2022).

In Dobermans, signs of ventricular arrhythmia can appear several months or even years before echocardiographic signs of DCM. In Boxers, ventricular ectopy is often detected 3 to 4 years before any clinical symptoms emerge. Other breeds that commonly show ventricular ectopy, where Holter monitoring could be beneficial, include Weimaraners and Great Danes, although specific guidelines for these breeds are not yet established. It's important to note that in all breeds, the presence of ventricular ectopy may indicate other possible underlying conditions, which should be ruled out (Dukes-McEwan et al., 2003). Also, the existence of an

accelerated idioventricular rhythm or ventricular escape complexes can not indicate DCM (Bussadori, 2023).

Consequently, a twenty-four-hour Holter exam is the preferred screening tool to be used for breeds like Boxers, Dobermans, and Great Danes (Wess, 2022). According to the latest screening guidelines for Dobermans, all males from 3-4 years of age should be submitted to the 24-hour Holter recording once a year and in females that exam should be done once in two years (Bussadori, 2023). That being so, occult DCM can be diagnosed in Dobermans when in a 24-hour Holter monitoring, more than 300 VPCs are identified or if two subsequent assessments within a year show 50 to 300 VPCs (Wess et al., 2017b). On the other hand, less than 50 VPCs in a 24-hour Holter exam are considered to be normal, however, any VPC recorded is a reason to be alert. Other authors believe that more than 100 VPCs in 24 hours is sufficient to diagnose DCM in Dobermans (Wess et al., 2017b). In addition, 1 VPC identified in a 5-minute ambulatory ECG is equivalent to more than 100 VPCs in a 24-hour Holter exam (Bussadori, 2023).

In the investigation of Martin et al. (2009), AF was reported in 45% of the dogs, VPCs were present in 31% of the cases and supraventricular premature complexes (SPVCs) showed a prevalence of 9%. AF was most frequently observed in giant and large dog breeds, including Irish Wolfhounds (94.1%), Great Danes (78.9%), Newfoundlands (77%), German Shepherds (73%), and Saint Bernards (72%). It was least common in Cocker Spaniels (8%). VPCs were most prevalent in Boxers (52.8%) and Dobermanns (44%). Supraventricular premature complexes (SVPCs) were most often found in Boxers (25%) and German Shepherds (14%). Only 11% of the dogs did not show any arrhythmia, and all of these dogs displayed either a QRS enlargement pattern associated with cardiomegaly or ST depression.

1.5.3.3 Echocardiography

The echocardiographic evaluation is believed to be the gold standard exam to diagnose canine DCM (Bussadori, 2023). In the clinical phase, systolic dysfunction and dilation of the left ventricle are two of the three major diagnostic criteria for DCM (Lobo, 2011;Wess, 2022). However, it should be mentioned these two characteristics are not specific for DCM (Dukes-McEwan et al., 2003). Echocardiography has a very high sensibility to detect myocardial dysfunction but is also useful to distinguish stages B1 from B2, as discussed later (Dukes-McEwan et al., 2003;Wess, 2022). In Dobermans, the echocardiographic view should always

be paired with a 24-hour Holter report, as this breed may show no clear echocardiographic abnormalities during the pre-clinical stage (Bussadori, 2023).

Usually, the veracity of the echocardiographic results relies on the quality of the examination (Wess et al., 2017b) and with 2D and M-mode echocardiography it´s possible to confirm the presence of myocardial dysfunction and chamber dilation (Dukes-McEwan et al., 2003). Nevertheless, a full echocardiogram adding color Doppler, with a simultaneous ECG, it´s crucial to rule out another congenital or acquired cardiac disease like patent ductus arteriosus, ventricular septal defect, mitral valve dysplasia, or myxomatous mitral valve degeneration, that have a similar phenotype with DCM (Dukes-McEwan et al., 2003;Wess et al., 2017b). Given the significant variation in dog body sizes, if breed-specific values are unavailable, it is recommended to use measurements that are allometrically scaled to body weight or body surface area (Bussadori, 2023). Nowadays, breed-specific values exist for Dobermans, Irish Wolfhounds, Great Danes and Newfoundlands (Bussadori, 2023).

Since diagnosing occult DCM is way more challenging, compared to clinical DCM, the European Society of Veterinary Cardiology created The ESVC Taskforce for canine DCM, proposing diagnostic guidelines for the disease (Dukes-McEwan et al., 2003). During the echocardiographic examination, the parameters of most relevance are dimensions of the left ventricle in systole and diastole, the distance between the peak of the E wave and the interventricular septum (EPSS), the sphericity index (SI), fractional shortening (FS) and the ventricular ejection fraction (EF) (Dukes-McEwan et al., 2003). Consequently, a dog is considered to have DCM if the end-diastolic volume index (EDV-I) >95 ml/m2; end-systolic volume index (ESV-I) >55 ml/m2; EPSS >6,5 mm; sphericity index <1,65; FS <20% and EF <40% (Wess et al., 2017b). The authors proposed a scoring system based on major and minor criteria, with each major criterion worth three points and each minor one point. The 3 major criteria recommended by the authors are: left ventricular M-mode systolic or diastolic dimensions, increased sphericity and either FS <20% or/and EF <40%. On the other hand, the authors recommended 6 minor criteria: arrhythmias, AF, increased EPSS, PEP:ET ratio increased, M-mode FS in equivocal range and left or bi-atrial enlargement. In this system, the sum of the scores should add up to a final score of 6 or more points in identifying a dog with DCM (Dukes-McEwan et al., 2003).

1.5.3.4 Biomarkers

Nowadays, cardiac biomarkers (CBM) like N-terminal pro-B-type natriuretic peptide (NT-proBNP) and cardiac troponin I (cTNI) can be helpful in the diagnosis of DCM, when exams such as echocardiography and Holter are not affordable to the patients (Oyama & Singletary, 2010;Wess, 2022). These biomarkers can be used in detecting the occult phase of DCM, diagnosing acute or chronic syndromes, evaluating the risk of developing cardiac congestive failure, monitoring the disease progression and help being a therapy and prognostic tool (DeFrancesco et al., 2002;Spratt et al., 2005;DeFrancesco et al., 2007;Boswood, 2009;Oyama & Singletary, 2010;Lobo, 2011). Currently, there are markers for myocyte injury, cardiac remodelling, endothelial dysfunction, inflammation and neurohumoral and hemostatic markers (Tarnow et al., 2007;Boswood, 2009). Recent reports recommend the use of both cTNI and NT-proBNP biomarkers since they complement each other (Boswood, 2009;Dukes-McEwan et al., 2022). However, they can not substitute Holter monitoring and echocardiography, since they work as an additional test (Wess, 2022).

As in human medicine, natriuretic peptides are seen as the most promising markers of cardiovascular disease in dogs (Boswood, 2009). This substances are released by the myocardium, mainly in response to an increased stress in the myocardial wall, and are therefore considered markers of myocyte stress (Oyama et al., 2007;Boswood, 2009). The NT-proBNP allows screening for DCM because it´s able to measure early cardiac enlargement, but it can not foretell ventricular arrhythmias with accuracy (Wess, 2022;Bussadori, 2023). This type of biomarker has been specially investigated in Dobermans and one study has shown that one BNP test can have a very high sensitivity (95,2%) and a low specificity (61,9%) to detect occult DCM (Oyama et al., 2007). In another report, the use of both NT-proBNP and a Holter exam allowed the identification of occult DCM with a sensitivity of 94,5 % and a specificity of 87,8%, leading to an accuracy of 91% in general (Wess, 2022). Further investigation needs to be done in other breeds and care must be taken when using these biomarkers, since NT-proBNP levels can be high because of other disorders like renal failure, pulmonary and systemic hypertension, sepsis as well as blood samples not being properly managed (Wess, 2022;Bussadori, 2023).

On top of that, troponins are intracellular proteins, which have shown to be highly specific and sensitive markers of myocyte cellular damage (Oyama & Solter, 2004;Wess, 2022). These biomarkers are the most widely used and have received special attention in clinical research in veterinary medicine (Lobo, 2011). This biomarker faces resembling restrictions, as

previously discussed for NT-proBNP, and there is insufficient evidence to support its use as a replacement for traditional methods like echocardiography and Holter monitoring (Wess, 2022). A study with cTNI demonstrated that the prognosis of dogs, with DCM and elevated cTNI concentrations, is worse than those with lower concentrations, which raises the possibility that troponins may have clinical utility in risk stratification (Oyama & Sisson, 2004).

In conclusion, CBM allows for early therapeutic intervention during the occult stage and the exclusion of affected dogs from breeding programs. The authors suggest annual CBM testing for Dobermanns to identify cases that may initially test negative. For a Dobermann with an abnormal CBM result, even if echocardiography and Holter monitoring show no abnormalities initially, follow-up testing after 12 months is crucial to detect emerging cases (Dukes-McEwan et al., 2022).

1.6. Clinical Staging

The first classification systems for heart disease, available to veterinarians, were made by the New York Heart Association (NYHA) and the International Small Animal Cardiac Health Council (ISACHC), focusing on data provided by complementary exams and clinical signs of heart failure (Atkins et al., 2009). The ISACHC system is divided into five classes: IA, IB, II, IIIA and IIIB. The first two classes, IA and IB, are an asymptomatic period where in IB there's the presence of radiographic and echocardiography abnormalities. The class II incorporates patients who develop clinical signs of heart failure, during moderate exercise and signs of CHF. The class III corresponds to a more advanced stage of heart failure with severe signs of CHF and can be subdivided into IIIA and IIIB, where IIIA includes patients that can be home treated and IIIB patients need to be hospitalized to have therapy (Petit et al., 2013). Despite these two classifications being used as semiquantitative schemes, they can be very subjective in terms of observation of clinical signs (Atkins et al., 2009).

Towards creating a more objective system, the American College of Veterinary Internal Medicine (ACVIM) created a classification for mitral valve disease staging, describing four basic stages: A, B, C and D. Stage A includes patients at high risk without heart murmurs and no identifiable structural heart disorder. Stage B incorporates patients that have structural heart disease, but remain asymptomatic and are further subdivided into B1 (no cardiac remodeling) and B2 (evidence of left-sided heart enlargement). Stage C involves patients who have past or current signs of heart failure due to structural heart

disease and stage D involves patients with advanced disease, in which symptoms of heart failure persist despite standard treatment (Atkins et al., 2009).

More recently, a new modified staging system for canine DCM was formed and includes five stages: A, B1, B2, C and D. Stage A encompasses dogs that have a predisposition to DCM, such as Dobermans, or that have tested positive for a genetic mutation associated with DCM. In stage B, there is the presence of morphological or electrical abnormalities, without clinical signs of heart failure, although syncope may occur. Besides, this stage can also be designed as the occult stage of DCM. This stage is further divided into two subgroups: B1 (presence of electrical abnormalities with normal echocardiographic measurements) and B2 (presence of arrhythmias with abnormal echocardiographic measurements). Stage C, also known as the overt stage, consists of dogs who present with either past or active signs of CHF, while stage D represents end-stage DCM with signs resistant to standard therapy. Early detection in Stage B is crucial for slowing the progression of the disease and preventing sudden cardiac death (Wess, 2022).

1.7. Treatment

The treatment of DCM has two major goals, which are delaying the beginning of CHF in dogs with occult DCM and dealing with the clinical signs of dogs in the overt phase of DCM (Bussadori, 2023). Since the undesired activation of neuroendocrine mechanisms, in the occult phase, is likely to worsen the DCM condition, drug treatments are needed to slow the progression to the overt phase of the disease (J. Elliott & Marr, 2001). Drugs, such as diuretics, positive inotropic drugs, β-blockers, angiotensin-converting enzyme (ACE) inhibitors and antiarrhythmics can be used in the therapy of DCM (Borgarelli et al., 2001;Bussadori, 2023). In a study performed by Martin et al., 2010, the association of multiple drugs is frequent, namely ACE inhibitors and furosemide. The approach to CHF must be individually conducted for each dog because no single drug or combination of drugs works for every dog or all stages of the disease (D. Sisson et al., 1999).

1.7.1. Diuretics

Diuretics such as furosemide are commonly used in cases in which CHF is present, especially when the dog develops pulmonary edema. However, if the dog presents a refractory response to the treatment of CHF, other diuretics are recommended such as hydrochlorothiazide, spironolactone and torsemide (Bussadori, 2023). Some authors believe that spironolactone should be administered even in the occult phase and this drug has been

shown, in humans, to diminish mortality and cardiac remodeling (Bussadori, 2023). Although there is no evidence of the role of spironolactone in dogs with CHF, it is thought that the use of this drug will block the high levels of aldosterone, which are high due to the activation of RAAS (O'Grady & O'Sullivan, 2004). With this being said, this medication could be used to decrease the development of DCM and delay the beginning of clinical signs of DCM in dogs (Bussadori, 2023). In a retrospective study with dogs with DCM, furosemide was applied more often in cases where the dog was in an advanced stage of the disease with signs of CHF (Martin et al., 2010). Controlling renal function and urine production is important when using diuretics because dogs affected by DCM are more likely to be vulnerable to prerenal azotemia (Bussadori, 2023).

1.7.2. Positive inotropic drugs

Once primary systolic dysfunction is inherent in DCM, the use of positive inotropic drugs has been referred to as one of the keys to DCM therapy (Borgarelli et al., 2001;Bussadori, 2023).

Drugs like dopamine or dobutamine, which can improve cardiac output, can be useful in treating severe CHF on the left side of the heart (Bussadori, 2023). Digoxin is also a positive inotropic and negative chronotropic agent which can block the RAAS and work partially as a diuretic. However, because this drug has many side effects, veterinarians usually prefer the use of pimobendan (Bussadori, 2023). Pimobendan is a benzimidazopyridazinone wich has both positive inotropic and vasodilating attributes (Honerjäger et al., 1984;Fujimoto, 1994). Because this drug has a both preload and afterload decrease effect, as well as better contractility of the myocardium, this substance diminishes the size of the heart in Dobermans with occult DCM (Summerfield et al., 2012). Since pimobendan is not affiliated with a higher oxygen demand, this drug is, at the moment, more desired to treat DCM than other positive inotropic substances like digoxin (Bussadori, 2023). In a study performed recently, the administration of pimobendan showed that this drug not only delayed the onset of CHF signs or sudden death in Dobermans with occult phase of DCM, by 9 months but also did extend the survival time of the dogs (Summerfield et al., 2012). Furthermore, the use of this substance didn't increase the occurrence of VPC's and has demonstrated a significant reduction in heart size, after 30 days (Summerfield et al., 2012). Another study, involving 81 dogs with DCM demonstrated that pimobendan alone or associated with benazepril was much more effective in the treatment of heart failure symptoms than benazepril itself (Borgarelli et al., 2001). In another report, therapy

with pimobendan showed significantly increased survival times in Dobermans affected with DCM but failed to show any improvements in the survival time in a group of Cocker Spaniels (Borgarelli et al., 2001). Despite that, data on the effects of pimobendan in other breeds are yet to be discovered, so further investigation about the treatment with this drug is recommended in dogs with occult DCM from other breeds (Summerfield et al., 2012;Bussadori, 2023).

1.7.3. Beta-blockers

This class of drugs is responsible for blocking the long-term bad effects of norepinephrine and, consequently, reversing the modifications in beta-adrenoreceptor numbers, usually seen in heart failure dogs (Borgarelli et al., 2001;J. Elliott & Marr, 2001). In human medicine, this type of medicament has shown benefits due to its capacity to grow the EF% in the long term, improve systolic function to expand the survival time of patients with DCM, as well as to enrich their quality of life and relieve the symptomatology (J. Elliott & Marr, 2001;Borgarelli et al., 2001;Bussadori, 2023). Some reports suggest carvedilol as well as other beta-blockers are efficient when associated with traditional therapies (Borgarelli et al., 2001). However, only a few studies report the use of this drug for the therapy of DCM and other investigations have demonstrated no improvement in using carvedilol in dogs (Borgarelli et al., 2001;Bussadori, 2023). Some authors believe the effectiveness of beta-blockers in dogs is lower, compared with humans, due to the rapid progression of DCM and worse signs of heart dysfunction in this species (Borgarelli et al., 2001). Having said that, the use of beta-blockers is not advised as a typical treatment for canine DCM (Bussadori, 2023).

1.7.4. ACE Inhibitors

During the years, has been questioned if ACE inhibitors are efficient when administrated in the occult phase of DCM or the overt phase. Some reports have shown that the use of these drugs in asymptomatic dogs with DCM can delay the onset of clinical signs of the disease (J. Elliott & Marr, 2001;Borgarelli et al., 2001;Bussadori, 2023). One potential explanation for this is that much of the RAAS activation occurs locally within the myocardium in the occult phase, instead of working in a systemic activation (J. Elliott & Marr, 2001;Bussadori, 2023). The effectiveness of preventive treatment in Dobermans is still uncertain, though one retrospective study suggests that benazepril may slow the progression of preclinical DCM in this breed (O'Grady et al., 2009;Summerfield et al., 2012).

Regarding the overt stage, studies have indicated positive benefits, of using ACE inhibitors to treat CHF in symptomatic dogs (Borgarelli et al., 2001). Despite most studies

showing progress in the patient's quality of life, the result in respect of the survival time has been doubtful, since most of the analysis included dogs with both DCM and myxomatous mitral valve disease (Bussadori, 2023). Three investigations have shown that ACE inhibitors may extend survival times in dogs with DCM compared to a placebo, though none of the studies reached statistical significance (Martin et al., 2010). On the other hand, the IMPROVE and COVE study demonstrated an overall clinical improvement in dogs receiving enalapril, compared to a placebo (D. D. Sisson, 1995;Woodfield, 1995;Borgarelli et al., 2001). Although these studies demonstrated a generally positive effect of ACE inhibitors on survival, this benefit disappeared when focusing only on dogs with DCM (Bussadori, 2023).

Having said that, ACE inhibitors are not commonly prescribed in the occult stage of DCM, but are part of the traditional chronic therapy in dogs with CHF, improving the quality of life of the affected patients (Summerfield et al., 2012;Bussadori, 2023).

1.7.5. Antiarrhythmic treatment

Since sudden death and the presence of VPCs are regularly seen in dogs with DCM, efforts to prevent this risk should be encouraged, especially if ventricular arrhythmias are followed by clinical signs such as weakness and syncope (O'Grady & O'Sullivan, 2004;Bussadori, 2023). For now, no reports have been able to confirm the efficacy of antiarrhythmic treatment in avoiding sudden death in dogs with preclinical DCM (O'Grady & O'Sullivan, 2004;Bussadori, 2023). Despite antiarrhythmic agents being administrated to reduce the risk of sudden death, some of these drugs are not efficient or can even increase this risk, in human medicine (O'Grady & O'Sullivan, 2004). Although class III antiarrhythmics have demonstrated some benefits in people, it is not clear if these agents can prevent sudden death in dogs (O'Grady & O'Sullivan, 2004). The drugs that are usually chosen in dogs are sotalol, mexiletine and amiodarone (O'Grady & O'Sullivan, 2004;Bussadori, 2023). Despite sotalol being a safer drug than amiodarone, further investigation is still necessary to determine its efficacy both in humans and dogs (O'Grady & O'Sullivan, 2004). Therapy with this medicament is also advised for dogs with preclinical DCM who have shown, in standard ECG or Holter exam, polymorphic ventricular arrhythmias or runs of ventricular tachycardia (Bussadori, 2023). In breeds like the Great Dane or Irish Wolfhound, AF is often observed, so with the administration of digoxin, diltiazem, or both together, it's possible to slow the ventricular response to an ideal ventricular rate of about 150 bpm (Bussadori, 2023).

1.8. Prognosis

To estimate the survival times of dogs with DCM it is necessary to know in which stage of the disease the dog is (occult or overt stage) and also if the dog was under treatment and in what stage he started doing therapy (TIDHOLM et al., 2001;Dukes-McEwan et al., 2003). In some reviews, therapy with ACE inhibitors and beta-blockers showed the possibility of interfering with the survival time of canine DCM (TIDHOLM et al., 2001). A research with benazepril demonstrated this drug could positively impact the survival time of DCM in dogs. However, further information is needed to know at what stage medication should be administered (Calvert et al., 1997). Despite the occult stage could last for years, the prognosis of dogs with CHF is usually poor (Wess et al., 2017b;Calvert et al., 1997).

The best independent prognostic factors, correlated with higher mortality, are pulmonary edema, pleural effusion, age, dyspnea, ascites, AF and bilateral heart failure (Monnet et al., 1995;Tidholm et al., 1997;Borgarelli et al., 2006). Another study proved that breed and echocardiographic indices of systolic function didn't show significance as independent prognostic indicators (Monnet et al., 1995;Dukes-McEwan et al., 2003). However, a report identified that Dobermans have a worse prognosis, in contrast with other breeds (Calvert et al., 1997) and another investigation reported that echocardiographic indices of left ventricular volume, except FS or EPSS, were prognostic markers in 31 dogs with DCM (TIDHOLM et al., 2001).

The median survival time can be different, depending on different studies, because some reports have included only dogs with CHF signs and other studies have included both dogs in the occult stage and the overt stage. For example, in a review made by Borgarelli et al. (2006), the median survival time, including dogs from both occult and overt stages, was 671 days. In other research, 25% of the dogs had died within 2 weeks after showing signs of CHF, more or less one-third passed away within the first month, and nearly two-thirds had died by the two-month mark (Calvert et al., 1997). Another review, showed a median survival time of 133 days, for all dogs with DCM. Furthermore, in this study, the survival rate for dogs with one year after being diagnosed with DCM was 28% and for dogs with two years was 14% (Martin et al., 2009). Also, another report showed that Dobermans at one year of the disease had a significantly low survival rate which may suggest the histophatological FID type has a worse prognosis than the AWF type of DCM (TIDHOLM et al., 2001). In a study made with affected Standard Schnauzers, it was demonstrated the onset of signs of CHF started at an early age,

being that males showed clinical signs of congestion earlier than females. The median survival time in this study, from the beginning of CHF until death, was 22 days, with males having a shorter survival time (13 days) than females (62 days) (Harmon et al., 2017). In another review with Irish Wolfhound dogs, it was displayed that dogs with CHF had a median survival time of nearly 7 months and dogs in the preclinical DCM stage, without echocardiographic abnormalities and with a sinus rhythm, had a median survival time of approximately, 29 months (C. Vollmar et al., 2019b). The authors also revealed that dogs with preclinical DCM who have started treatment early, in general, showed a delay in CHF signs and had a prolonged survival time (C. Vollmar et al., 2019b). Another research with 367 dogs with DCM showed that the survival time was different for each breed (Martin et al., 2010). Great Danes and Dobermans were revealed to have a shorter life, 5 weeks and 10 weeks, respectively, with Golden and Labrador Retrievers having a median survival of 30-35 weeks and Cocker Spaniels living longer with 82 weeks (Martin et al., 2010).

Dogs affected with DCM can die in two possible ways: sudden cardiac death or progressive congestive heart failure (Monnet et al., 1995). This author believes these two outcomes can have distinct prognostic indicators, where VPCs can predict sudden death and indices of cardiac function can foresee a death due to CHF (Monnet et al., 1995). In the research made by Martin et al. (2009), 51% of the dogs were euthanased due to cardiac problems, 40% died either because of CHF or arrhythmia, 6% were still alive at the end of the study and 3% died due to non-cardiac causes. In another report, with Doberman Pincher dogs, the cause of death was revealed to be 33% CHF, 29% euthanasia and 33% sudden death (Petric et al., 2002).

1.9. Objectives

Several retrospective studies on DCM have been published, differing in the countries where they were performed, the number of dogs, and the different breeds involved.(Monnet et al., 1995; Tidholm et al., 1997;Martin et al., 2009;Martin et al., 2010;Freid et al., 2021).

The goal of the dissertation was to perform a retrospective study of DCM in Portugal and therefore, to compare the results obtained with those published to date. With this being said, the author intended to analyze the prevalence of the disease in different breeds, sexes, and ages. Also, the author compared different clinical presentations, radiographic alterations, echocardiographic measurements and all pathological alterations worthy of note. Besides that, the author identified the prognostic values of the different variables under study, estimated survival times and determined which variables influence them the most.

2 Materials and Methods

2.1 Database and procedures

The database was formed with Microsoft Excel, including only cases of dogs that were diagnosed for the first time with DCM. The diagnosis was made according to the clinical presentation and also with echocardiographic and Holter examination. This database can be divided into three phases: identification of the animal, echocardiographic measurements and clinical history.

2.1.1 Identification

All animals were respectively identified with the name, number of identifications attributed to each animal (ID), date of birth, date of echocardiographic exam, breed, weight and sex.

2.1.2 Echocardiographic measurements

Echocardiography was always performed by the same operator, using the VIVID 3 system (GE Medical Systems), esaote mylab seven and esaote mylab X8. It was used multifrequency sector probes between 3 and 5 MHZ and without any type of chemical administration. To this end, was used a two-dimensional (2D) or B mode, M mode and color and spectral (pulsed and continuous) Doppler modes, the latter being essential in assessing blood flow at the level of all heart valves.

The echocardiographic measurements analyzed with M Mode included: interventricular septal thickness at end-diastole (IVSd), left ventricular internal dimension at end-diastole (LVIDd), left ventricular posterior wall thickness at end-diastole (LVPWd), interventricular septal thickness at end-sistole (IVSs), left ventricular internal dimension at end-systole (LVIDs), left ventricular posterior wall thickness at end-systole (LVPWs), ejection fraction (EF), fractional shortening (FS) and EPSS.

Applying the B Mode, was possible to determine the diameter of the aorta (Ao) and the left atrium (LA), with the ratio being calculated (LA/Ao). Furthermore, other measurements were made: the area of the left ventricle at end-diastole (LVAd) and end-systole (LVAs), the left ventricle length at end-diastole (LVLd) and end-systole (LVLs), the sphericity index (SI) together with M-mode, the left ventricular volumes at end-diastole (LVEDV) and end-systole (LVESV), the left ventricular ejection volume (LVEV) and ejection fraction (LVEF), the heart

rate (HR) and, finally, the end-diastolic volume index (EDV-I) and end-systolic volume index (ESV-I) were estimated according to body surface area (BSA).

Through the application of Doppler, it was possible to analyze the blood flow at the level of the different valves. Placing the Doppler in the aorta, it was estimated the peak blood flow at the level of the aorta (AVpeak), the peak aortic pressure gradient (AVpeakPG), the pre-ejection period (PEP), the ejection time in the left ventricle (LVET) and the ratio PEP/LVET. When putting the Doppler at the level of the pulmonary valve, it was registered the peak blood flow of the pulmonary valve (PVpeak) and the peak pulmonary pressure gradient (PVpeakPG). Positioning the Doppler in the mitral valve, it was registered the peak velocity of the waves E (Epeak) and A (Apeak), the E/A ratio, the E wave deceleration time (EWDT) and, in some cases, the mitral regurgitation peak velocity (RMVpeak) and peak gradient (RMVpeakPG). It was also seen at the level of the tricuspid valve, the regurgitation peak velocity (RTVpeak) and peak gradient (RTVpeakPG), when regurgitation was present. In conclusion, the transmitral flow (TMF) pattern of the animals was classified as restrictive or non-restrictive patterns, as recommended by Borgarelli et al. (2006). With this being said, dogs were classified with a restrictive pattern if they had an E/A ratio higher or equal a two or if they had an E/A ratio between one and two, with an E wave deceleration time equal or less than 80 milliseconds (ms). Also, if the dog showed AF and an E wave deceleration time less or equal to 80 ms, he was classified as having a restrictive pattern. On the contrary, if the dog had an E/A ratio less than 1, he was automatically considered to have a non-restrictive pattern (Borgarelli et al., 2006).

2.1.3 Clinical history

The clinical history was the third step of the study, where the author collected the following parameters from the database: heart murmur, cardiomegaly, mitral insufficiency (MI), tricuspid insufficiency (TI), pulmonary insufficiency (PI), aortic insufficiency (AI), pulmonary hypertension (PH), cough, dyspnea, inappetence, exercise intolerance, syncope, ascites, pulmonary edema and pleural effusion. All these parameters were classified as present (P) or absent (A) through clinical presentation.

Besides that, the author pointed out if the cause of the death was by cardiac reasons or non-cardiac reasons and if the dogs were submitted to euthanasia or not. The day of the death was registered and the survival time was obtained in days, by subtracting the day the dog died from the day he was diagnosed with DCM. Through an in-house ECG or a Holter monitoring, the author verified the presence of arrhythmias: AF, VPCs, SVPCs, supraventricular

tachycardia (SVT), sinus arrhythmia (SA), atrial ventricular block (AVB), left bundle branch block (LBBB), ventricular tachycardia (VT), sinus tachycardia (ST), sinus arrest (SAR) and ventricular escape beat (VEB). If the dog didn´t have an arrhythmia, he was classified as having a sinus rhythm (SR). The author followed a modern modified staging system to categorize each animal with the respective stadium of the disease: A, B1, B2, C and D (Wess, 2022).

2.2 Statistical analysis

The statistical variables analyzed throughout this dissertation are divided into 21 discrete variables (breed, sex, restrictive pattern, murmur, cardiomegaly, ECG, cause of death, MI, TI, PI, AI, PH, cough, dyspnea, exercise intolerance, inappetence, syncope, ascites, pulmonary edema, pleural effusion and staging system) and 42 continuous variables (weight, age at diagnosis, survival time, IVSd, LVIDd, LVPWd, IVSs, LVIDs, LVPWs, EF, FS, EPSS, Ao, LA, LA/Ao, LVAd, LVAs, LVLd, LVLs, SI, LVEDV, LVESV, LVEV, LVEF, HR, EDV-I, ESV-I, AVpeak, AVpeakPG, PEP, LVET, PEP/LVET, PVpeak, PVpeakPG, Epeak, Apeak, E/A ratio, EWDT, RMVpeak, RMVpeakPG, RTVpeak and RTVpeakPG).

Statistical and graphical analyses were performed by using the IBM SPSS Statistics. The relationship to survival of 14 clinical, ECG and echocardiographic variables (class of CHF according to Wess classification, pulmonary edema, pleural effusion, sex, dyspnea, ascites, AF, VPCs, breed, FS, EF, EPSS, ESV-I, EDV-I and TMF pattern) was evaluated. To classify dogs with similar risk profiles, we established arbitrary cutoff points optimized for distinguishing between patient groups.

Survival curves, median survival times, and 95% CIs were obtained by the Kaplan-Meier method and the Hazard function. Differences between survival curves were tested by the log-rank test (a =0,05). Survival time was measured from the date of DCM diagnosis at Hospital Veterinário do Porto to either the date of death or the study's endpoint, for which 04/11/2024 was considered.

3 Results

A retrospective study was conducted in Portugal at the Hospital Veterinário do Porto, where was observed, between February 2001 and July 2024, a sample of 163 medium to large-sized pure-bred dogs diagnosed with DCM (120 males and 43 females), except the Cavalier King Charles Spaniel (1 dog), the Cocker Spaniel (8 dogs) and non-specific breed (NSB) patients (14 dogs).

3.1 Population characterization

This dissertation involved 163 dogs, where 26 different breeds and NSB dogs were studied. Table 1 shows the number of dogs per breed, observed in the study. The breeds identified in the study were: Boerboel, Boxer, Bull Terrier, Cane Corso, Portuguese Water Dog, Transmontano Mastiff, Pyrenean Mountain Dog, Cavalier King Charles Spaniel, Cocker Spaniel, Dalmatian, Doberman Pincher, Great Dane, Bordeaux Mastiff, Fila Brasileiro, Golden Retriever, Labrador Retriever, Neapolitan Mastiff, Old English Sheepdog, German Shepherd, Portuguese Pointer, American Pit Bull Terrier, Rafeiro Alentejano, Rottweiler, Saint Bernard, Estrela Mountain Dog and Newfoundland

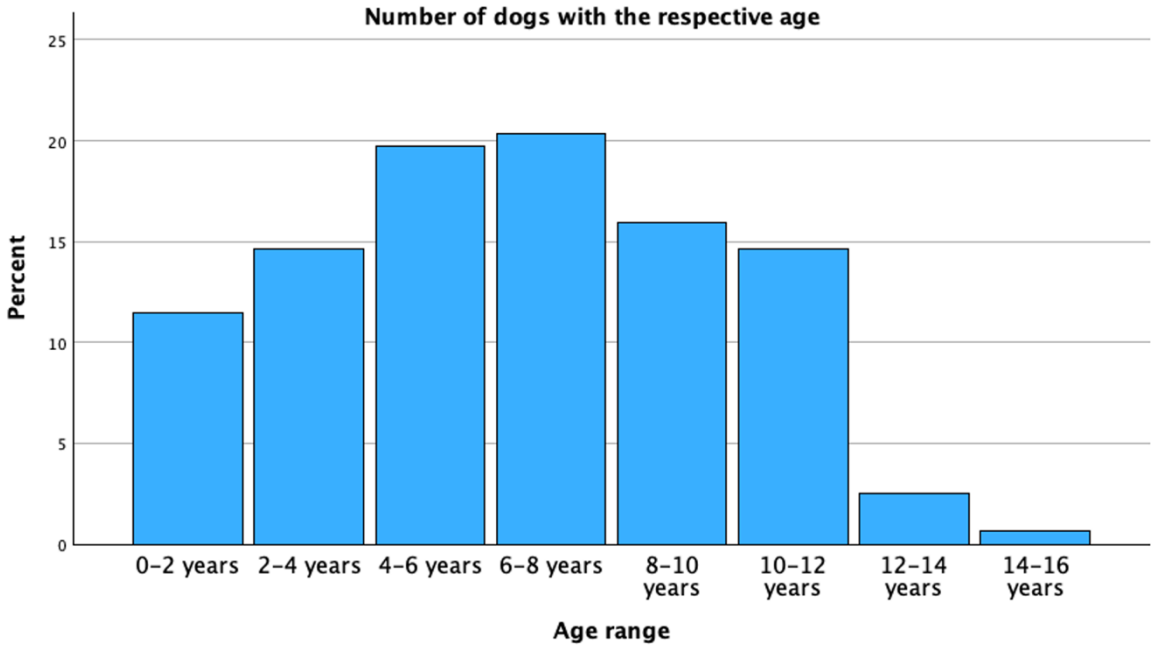
The mean age of diagnosis with DCM was 7 years ± 41 months, with a minimum age of approximately 2 months for a Boxer and a maximum of 15 years for an NSB dog. The average weight was 40.7 kg ± 15,4 kg, with the minimum weight being 10 kg in a Cocker Spaniel and the maximum being 74.5 kg in a Saint Bernard.

Table 1 – Number of dogs per breed

Breed	**Number of dogs**	**Breed**	**Number of dogs**
Estrela Mountain Dog	34	German Shepherd	2
Boxer	29	Portuguese Pointer	2
Doberman Pincher	22	Rottweiller	2
NSB	15	Boerboel	1
Great Dane	10	Bull Terrier	1
Cocker Spaniel	8	Cane Corso	1
Saint Bernard	6	Portuguese Water Dog	1
Bordeaux Mastiff	4	Cavalier King Charles Spaniel	1
Golden Retriever	4	Fila Brasileiro	1

Labrador Retriever	4	Neapolitan Mastiff	1
Pyrenean Mountain Dog	3	Old English Sheepdog	1
Dalmatian	3	American Pit Bull Terrier	1
Newfoundland	3	Rafeiro Alentejano	1
Transmontano Mastiff	2		

Seventy-four percent of the dogs were male (120) and 24 percent were female (43), with male to female ratio being 2,8:1. It was possible to compare the ratio for some breeds, like for example the Boxer (2,6:1), the Doberman (2,7:1), the Estrela Mountain Dog (3,2:1) and for the NSB dogs (2:1). However, for the other breeds it wasn´t possible to determine the ratio, since the number of dogs was too low.



Graph 1 – Number of dogs per age.

3.2 Clinical signs

3.2.1 Anamnese

The signs more commonly reported by the owners were exercise intolerance (30,7%), lack of appetite (30,1%), dyspnea (25,8%), cough (21,5%) and only 7,4% manifested having at

least one episode of syncope. Furthermore, a murmur was identified in 23,3% of the dogs, during the clinical examination.

Table 2 – Number of dogs per clinical sign

Anamnese	Number of dogs
Exercise Intolerance	50
Lack of Appetite	49
Dyspnea	42
Murmur	38
Cough	35
Ascites	34
Syncope	16

3.2.2 Radiographic findings

Signs of CHF were also observed, for example, ascites (20,8%), pulmonary edema (18,4%) and pleural effusion (9,2%). The dogs were also exposed to radiography examination measured objectively, using the cardiac vertebral index, where 15,9% of the dogs reported cardiomegaly. According to the Wess classification, from the dogs that did have information about their heart failure stage (n=122), 11,5 % of the animals were in stage B1, 32,8 % in stage B2 and 55,7 % in stage C or D.

Table 3 – Number of dogs per radiographic finding

Radiographic finding	Number of dogs
Pulmonary Edema	30
Cardiomegaly	26
Pleural Effusion	15

3.3 Electrocardiographic abnormalities

The patients were submitted either to an in-house ECG or to a Holter examination, where a mean of 147 bpm (tachycardia) was registered and also a median of 142 bpm with the minimum being 44 bpm and the maximum of 300 bpm. Of the 163 dogs diagnosed with DCM, 84 (51,5%) showed significant electrocardiography abnormalities and 79 (48,5%) demonstrated to have an SR. Within the 51,5% of the dogs with abnormalities detected in the ECG, 37

(22,7%) showed AF, 32 (19,6%) showed VPCs, 5 (3,1%) had SA, 3 (1,8%) had both AF and VPCs, 3 (1,8%) had SVT, 1 (0,6%) had ST, 1 (0,6%) had SVPCs, 1 (0,6%) had SAR and 1 (0,6%) had VEB. In the 32 (19,6%) dogs who present VPCs, 29 (17,9%) have shown this arrhythmia alone, 1 (0,6%) dog had a VPC and AVB of first degree, 1 (0,6%) dog had a VPC and LBBB and 1 (0,6%) dog had a VPC, LBBB and VT.

Table 4 – Number of dogs per arrhythmia

Arrhythmia	**Number of dogs**
AF	37
VPCs	32
SA	5
AF and VPCs	3
SVT	3
ST	1
SVPCs	1
SAR	1
VEB	1

3.4 Echocardiographic abnormalities

All echocardiographic values with the respective mean, standard deviation, median, minimum and maximum can be found on Table 5.

Table 5 – Echocardiographic variables

Number of dogs	Variable	Mean ± SD	Median	Minimum	Maximum
N=160	IVSd (mm)	10,2±0,2	9,8	1,9	16,2
N=157	LVIDd (mm)	57,7±1,1	56,4	19,2	96,7
N=159	LVPWd (mm)	10,1±0,2	10,0	2,8	20,7
N=159	IVSs (mm)	12,8±0,4	11,7	4,1	52,7
N=156	LVIDs (mm)	47,5±1,1	45,4	10,8	89,1
N=158	LVPWs (mm)	12,6±0,2	12,5	6,3	23,6

N=70	EF (M mode) (%)	38,6±1,9	37,3	12,0	99,8
N=140	FS (%)	19,3±0,9	17,4	1,7	91,7
N=75	EPSS (mm)	14,7±1,0	13,4	1,7	43,1
N=145	Ao (mm)	23,0±0,4	23,3	2,2	37,5
N=145	LA (mm)	42,1±1,0	41	4,7	75,8
N=145	LA/Ao	1,89±0,05	1,8	0,9	4,0
N=65	LVAd (cm^2)	32,1±1,5	30,5	14,2	65,4
N=65	LVAs (cm^2)	24,5±1,3	23,2	10,0	56,3
N=128	LVLd (mm)	70,7±1,2	72,3	38,5	97,6
N=65	LVLs (mm)	60,8±1,5	61,1	39,8	93,2
N=126	SI	1,262±0,02	1,25	0,80	2,65
N=124	LVEDV (ml)	150,3±7,5	130,2	34,2	410,6
N=123	LVESV (ml)	102,8±6,2	82,2	6,0	352,9
N=123	LVEV (ml)	47,6±2,4	44,6	-0,1	123,8
N=147	LVEF (%)	33,5±1,3	32,9	5,3	89,1
N=98	HR (bpm)	147±6	142	44	300
N=111	EDV-I (ml/m^2)	126,1±5,7	117,3	31,4	322,0
N=110	ESV-I (ml/m^2)	84,9±4,8	72,2	6,7	260,0
N=126	AVpeak (m/s)	1,21±0,05	1,17	0,43	4,46
N=60	AVpeakPG (mmHg)	6,34±0,8	5,1	0,7	35,7
N=41	PEP (msec)	76,2±3,2	70,0	35,0	128,0
N=41	LVET (msec)	142,4±4,5	138,0	99,0	225,0
N=41	PEP/LVET	0,56±0,03	0,54	0,22	0,99
N=139	PVpeak (m/s)	0,92±0,04	0,81	0,35	3,56
N=65	PVpeakPG (mmHg)	3,44±0,3	2,6	0,5	12,5
N=122	Epeak (m/s)	1,06±0,04	0,98	0,21	3,84
N=62	Apeak (m/s)	0,63±0,03	0,59	0,31	1,16
N=61	E/A ratio	1,42±0,08	1,34	0,49	3,58

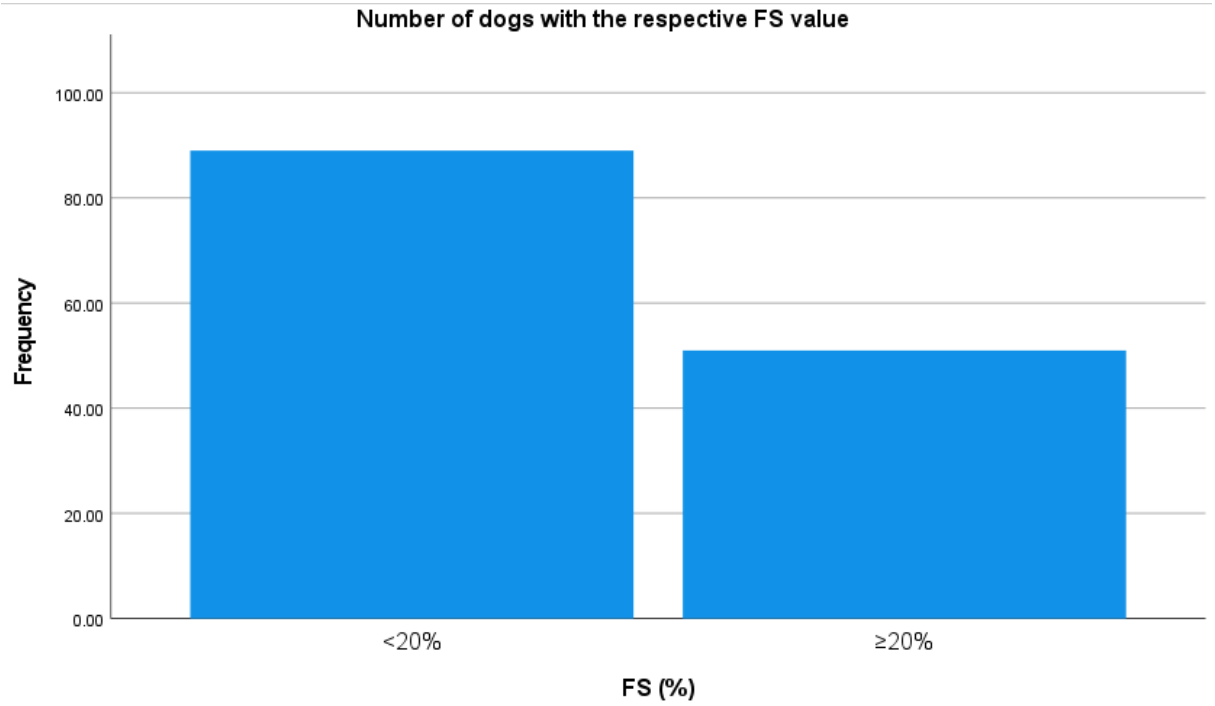
N=47	EWDT (ms)	90,5±4,9	85,0	32,0	183,0
N=27	RMVpeak (m/s)	4,29±0,24	4,57	1,30	6,02
N=27	RMVpeakPG (mmHg)	79,3±7,4	7,0	6,8	144,8
N=43	RTVpeak (m/s)	2,48±0,11	2,58	0,90	3,80
N=43	RTVpeakPG (mmHg)	26,7±2,1	26,6	3,2	57,8

During the echocardiographic evaluation, secondary valve insufficiencies were observed in some dogs with DCM. Table 6 shows the number of animals that presented MI, TI, PI, AI and PH. In the 163 dogs of the study, MI was reported in 107 dogs (65,6 %), TI in 70 dogs (42,9 %), PI in 35 dogs (21,5 %), PH in 24 dogs (14,7 %) and AI in 14 dogs (8,6 %). Also, some dogs showed more than one valve insufficiency, simultaneously.

Table 6 – Number of dogs per valve insufficiency

Valve Insufficiency	Number of dogs
MI	107
TI	70
PI	35
PH	24
AI	14

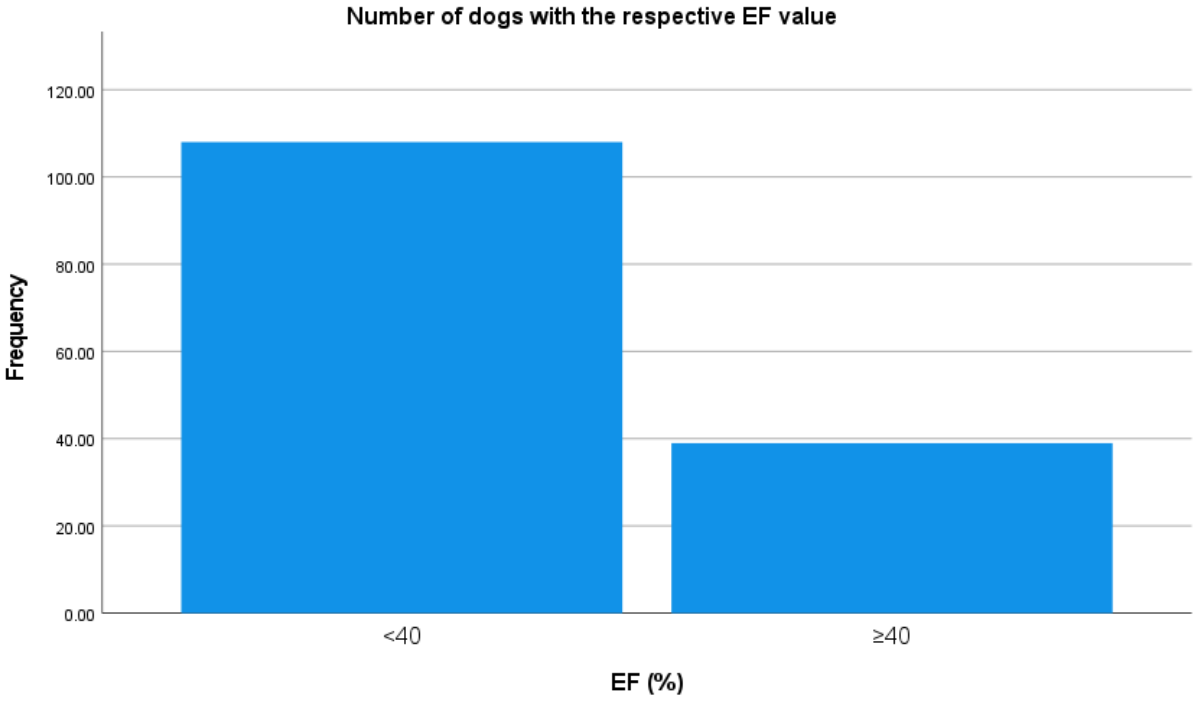
For the diagnosis of DCM, echocardiographic parameters such as FS, EF, EDV-I, ESV-I and EPSS are important to analyze systolic dysfunction and chamber dilation. The author observed the relative frequency of these parameters, according to the cutoff values of ESVC. Graph 2 shows the frequency of animals in the study in which the FS, determined by M-mode, was below or above 20%.



Graph 2 – Number of dogs with the respective FS value

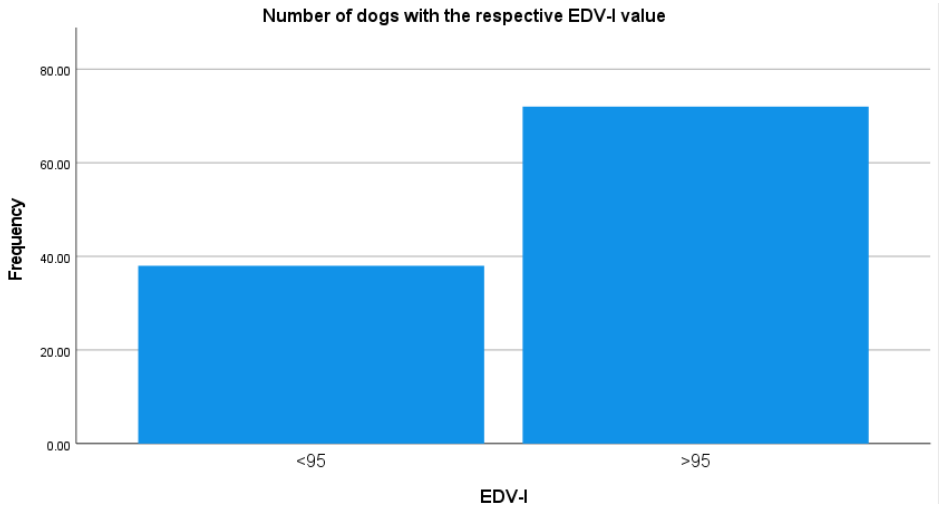
It is possible to observe in Graph 2 that 89 dogs (63,6%) had an FS below 20% and 51 dogs (36,4%) had an FS greater than or equal to 20%.

In Graph 3 the author presents the number of dogs in which the percentage of the EF, determined by the Simpson method, was below or above 40%. It is evident that 108 dogs (73,5%) had an EF below 40% and 39 dogs (26,5%) had an EF greater than or equal to 40%.

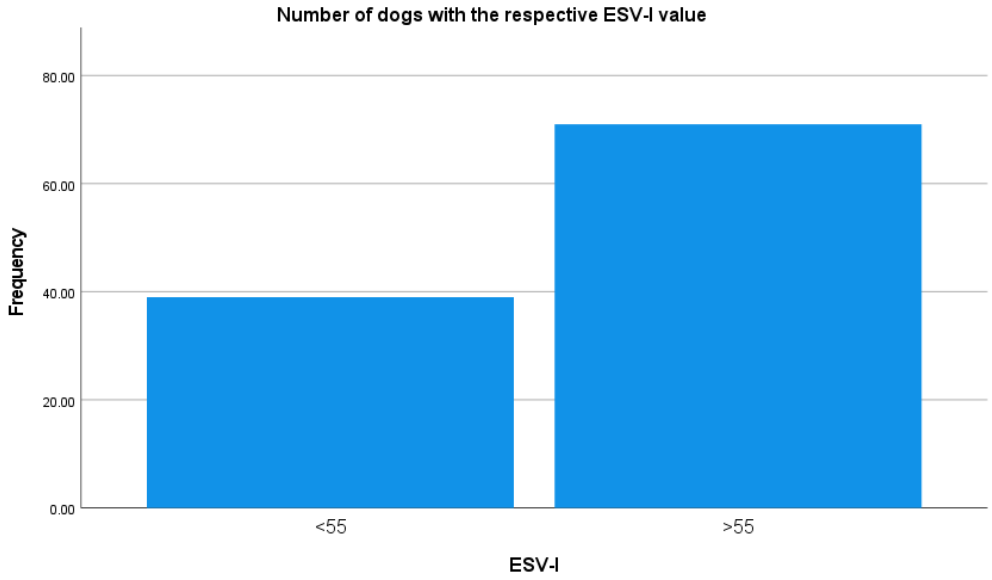


Graph 3 – Number of dogs with the respective EF value

In Graph 4, it is expressed the number of dogs, where the EDV-I value was below or above 95 ml/m2. In this parameter, 38 dogs (34,5%) had an EDV-I below 95 ml/m2, and 72 dogs (65,5%) had an EDV-I greater than 95 ml/m2. Also, graph 5 represents the number of dogs in which the ESV-I was below or greater than 55 ml/m2, being that 39 dogs (35,5%) had an ESV-I value below 55 ml/m2 and 71 dogs (64,5%) had an ESV-I greater than 55 ml/m2.

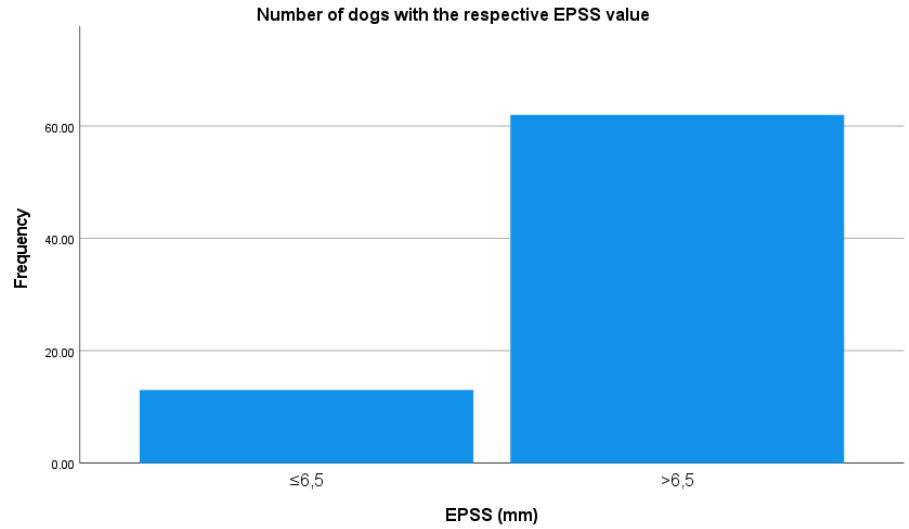


Graph 4 – Number of dogs with the respective EDV-I value



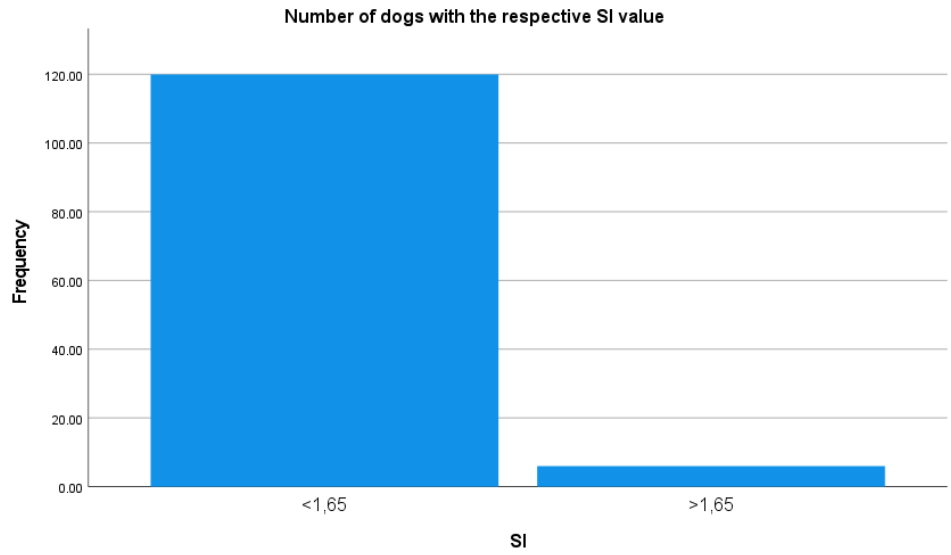
Graph 5 – Number of dogs with the respective ESV-I value

The EPSS was another echocardiographic parameter measured and the graph 6 shows the number of animals that had an EPSS value below or above 6,5 mm. According to the results, 62 dogs (82,7%) showed to have EPSS value greater than 6,5 mm and 13 dogs (17,3%) had less than or equal to 6,5 mm.



Graph 6 – Number of dogs with the respective EPSS value

Finally, the graph 7 presents the number of dogs with a sphericity index below or above 1,65. The results demonstrate that 120 dogs (95,2%) had an SI lower than 1,65 and 6 dogs (4,8%) had an SI greater than 1,65.



Graph 7 – Number of dogs with the respective SI value

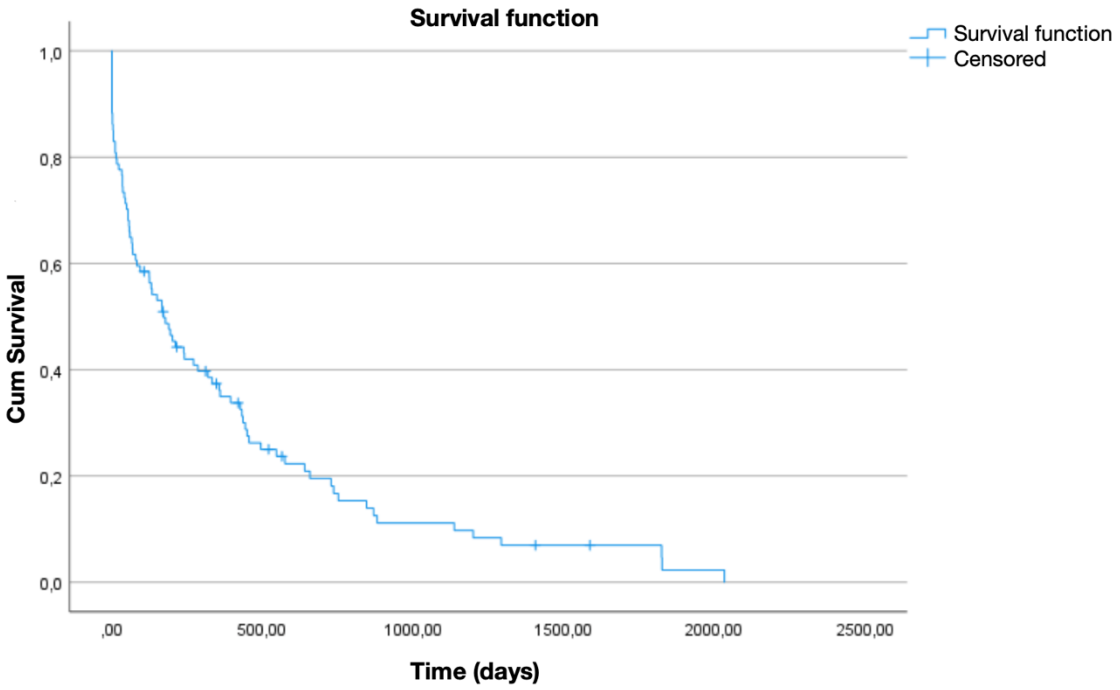
3.5 Survival time

According to the survival time, it was possible to access a total of 94 dates of death in the population of dogs with DCM. Of the 94 dogs, only 46 (49,0 %) dogs have information if the death was cardiac or non-cardiac and if the dog was euthanized or non-euthanized; 38 dogs (40,4%) have no record of the way of death and 10 dogs (10,6%) were still alive and, therefore, the day 04/11/2024 was attributed as the date of death, which coincided with the end of this study. These 10 dogs were included in the survival analyses and thereafter censored. With this being said, from the 46 dogs who were possible to follow up the way of death, 41 dogs (89,1%) died due to cardiac reasons and 5 (10,9%) died due to non-cardiac reasons. Also, 23 dogs (50,0%) were euthanized and 23 dogs (50,0%) were non-euthanized. Of the 41 dogs who died from cardiac reasons, 18 dogs (43,9%) were euthanized and 23 (56,1%) were non-euthanized. Of all the dogs that were possible to know the follow-up (n=46), 39,1% were euthanized due to cardiac reasons.

The mean survival time was 335 days (48 weeks) ± 444 days, the median was 170 days, the minimum was 1 day and the maximum was 2033 days. To evaluate the survival time, the author accessed the Kaplan-Meier method from which is possible to analyze the survival curve (graph 8) and the Hazard accumulation function (graph 9). In graph 8, the y-axis (cumulative survival) shows the cumulative survival probability, ranging from 1 (100% of dogs alive) to 0 and the x-axis (time) represents the time in days after the diagnosis of DCM. Analyzing the curve of survival, the line starts at the top (1.0), indicating that all dogs are alive at the time of diagnosis followed by an emphasized reduction on the first days after the dogs

have received the diagnosis of DCM, showing a high mortality rate soon after diagnosis. This can be explained because 11 dogs (11,7%) died in one day since they arrived at the hospital in a very advanced stage of the disease. Also, 19 dogs (20,2%) died in the first 15 days, which means that 79,8% of the dogs were alive in the first two weeks after the diagnosis with DCM. The curve tends to gradually fall, especially after 600 days where, approximately, 20% of the dogs are still alive, which indicates that while many dogs die soon after diagnosis, some survive for longer periods. Furthermore, the percentage of dogs that are alive in one year is about 30% and in two years is about 14%.

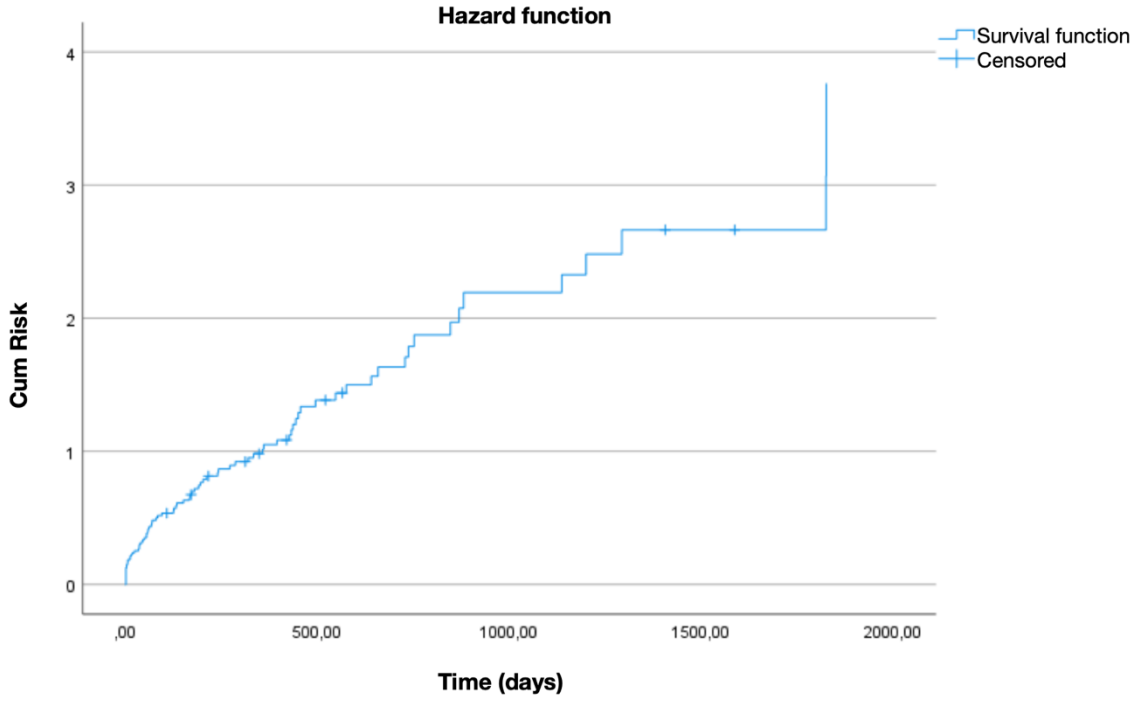
The survival time of animals whose follow-up got lost was censored and therefore were not included in the study sample. For dogs that remained alive until the end of this study, survival time was estimated until 04/11/2024, the date set for the conclusion of this study.



Graph 8 – Survival function of dogs per day

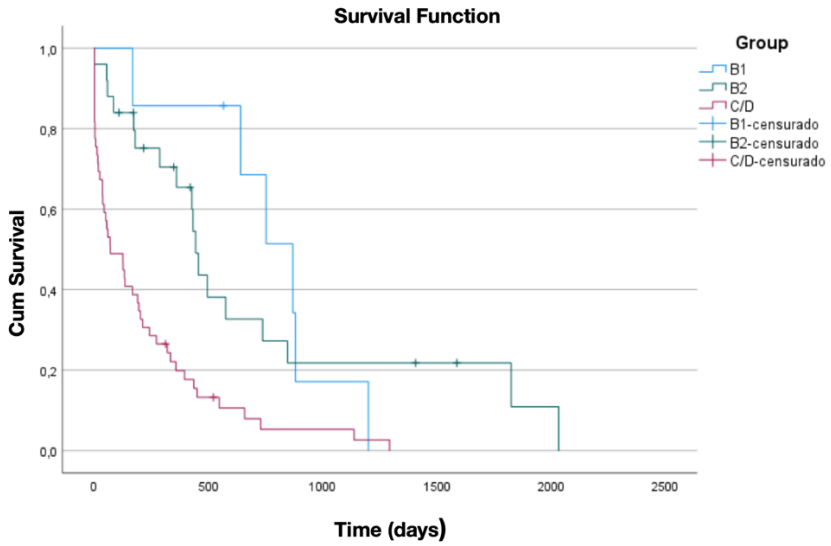
Using the hazard function in graph 9, it's possible to see a very rapid increase in the accumulated risk immediately after the diagnosis, meaning that the risk of death in the early days after the diagnosis is high. The curve is progressively slowing down afterward, until it becomes constant a little bit before 1500 days, which means the risk of death around that period

doesn't get higher. In general, as it's expected, the accumulated risk in the graph is getting bigger, in the course of time.



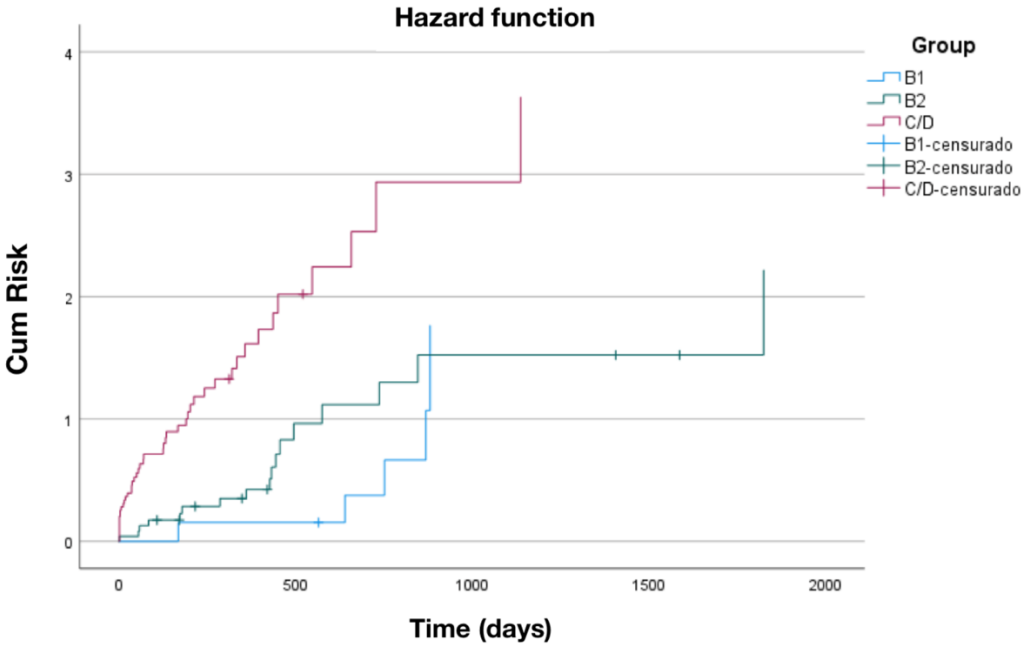
Graph 9 – Accumulated risk of death per day

The survival analysis may not be the same, depending on the severity of the disease. The author added the dogs to their respective class of disease (B1, B2 and C/D), using the Kaplan-Meier method to determine the survival curve of dogs, in the function of the severity of the disease (P=0,000). In graph 10 we found that the curve from group C/D declines more sharply than those of the other two groups and that the curve from group B2 decreases more quickly than the curve from group B1. With this being said, the dogs in stage C have the worst prognosis, followed by the dogs in stage B2 and finally, the dogs in stage B1 have the best prognosis, compared with the other two groups. In group B1, the mean survival time was 725 days and the median was 752 days. In group B2, the mean survival was 549 days and the median was 420 days. In group C/D, the mean survival was 209 days and the median was 129 days.



Graph 10 – Survival function according to the stage of disease

The hazard functions of the three classes show a behavior opposite to that of the survival curves. In other words, the hazard curve from group C has a higher value and the curve from group B1 the lowest, as can be seen in graph 11 below (P=0,000). In conclusion, the dogs classified with stage C have a higher risk of death and the dogs in stage B1 have the lowest risk of death. The dogs from stage B2 have a lower risk of death than the dogs from stage C and a higher risk than the dogs from stage B1. Both curves have a null P value which shows these results are statistically significant.

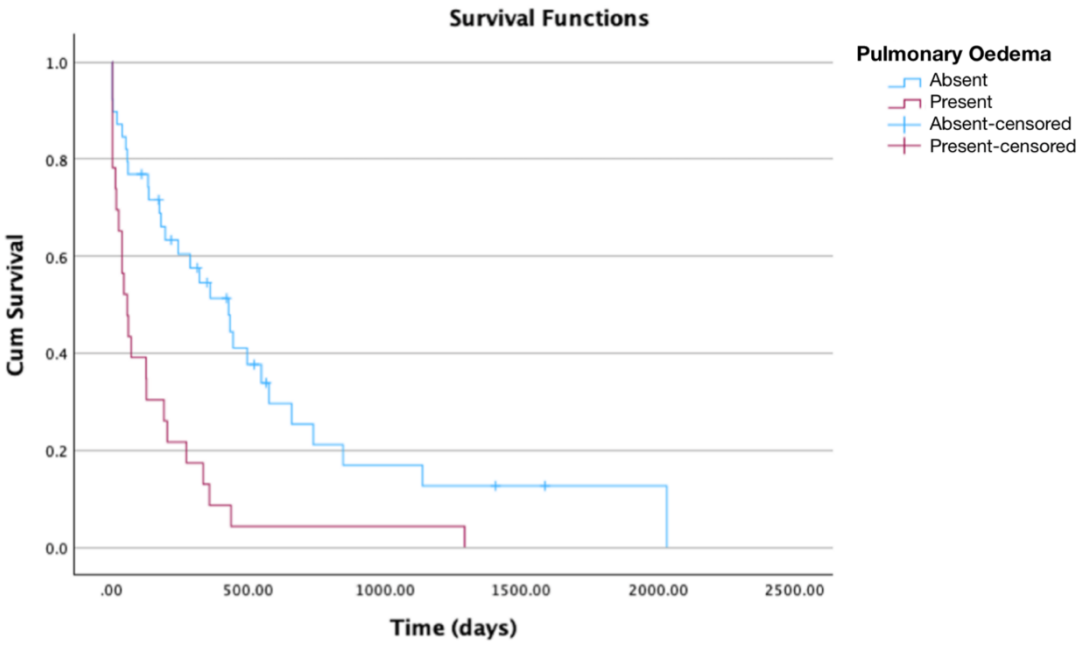


Graph 11 – Accumulated risk of death according to the stage of disease

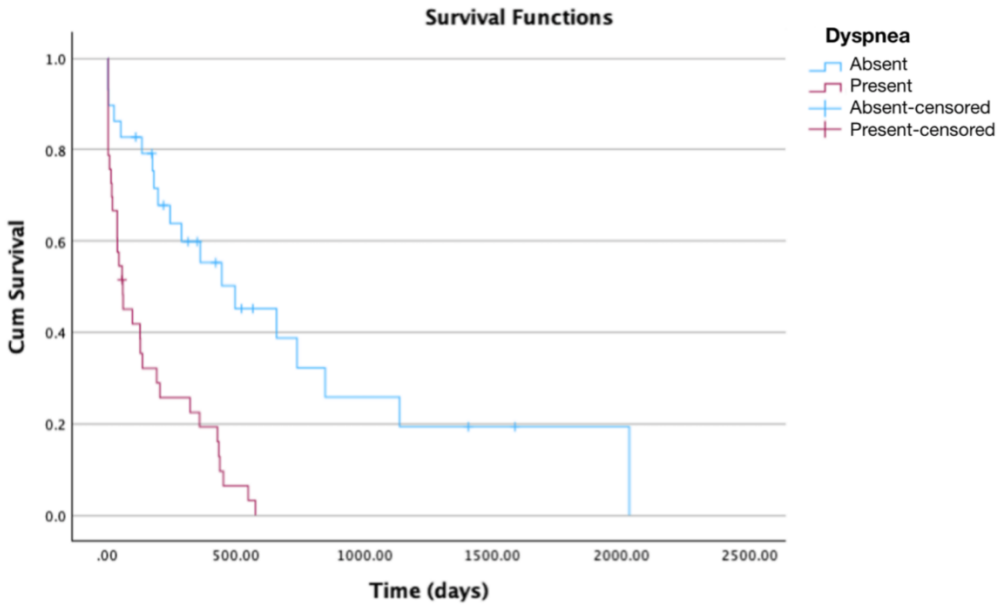
3.6 Prognostic indicators

In this dissertation, the author analyzed independent prognostic variables like pulmonary edema, pleural effusion, sex, age, dyspnea, ascites, AF, VPCs and breed. On the other hand, echocardiographic prognostic parameters were also considered such as FS, EF, EPSS, ESV-I, EDV-I and TMF pattern.

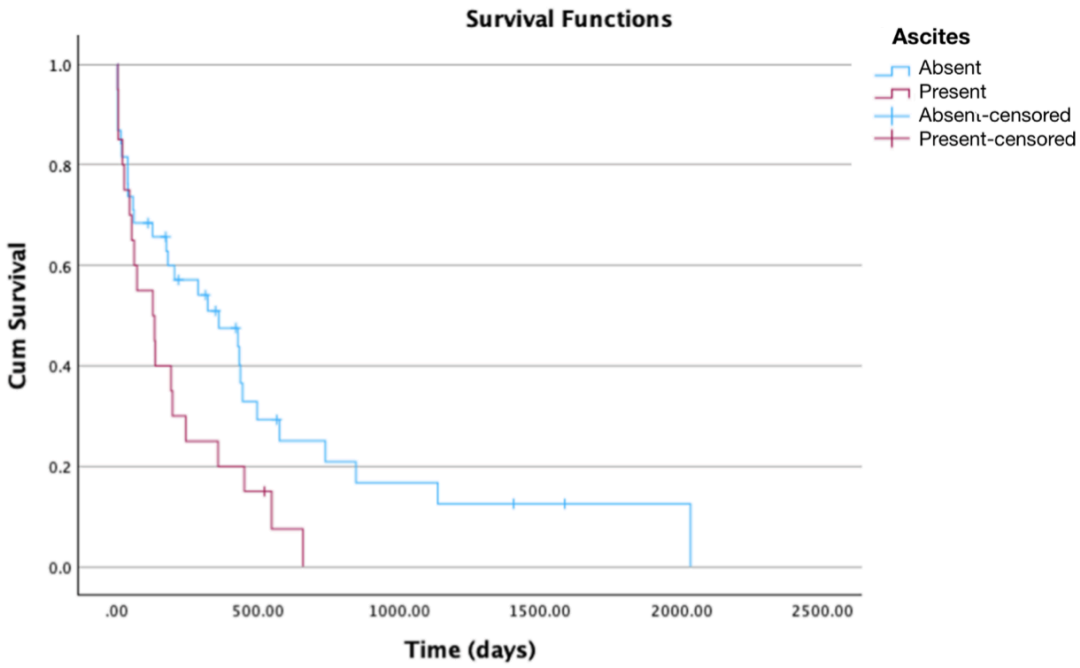
Concerning the radiographic findings, pulmonary edema (P<0,001), dyspnea (P<0,001) and ascites (P=0,037) were demonstrated to be significant and negatively associated with survival. The variable pleural effusion was also studied but revealed not to be statistically significant (P=0,104), although the results of this variable were negatively associated with survival. Regarding the electrocardiographic findings, AF (P=0,145) and VPCs (P=0,906) were not statistically significant, although dogs with AF showed a worse prognosis. The factor breed was not statistically significant in the study (P=0,968) as well as the factor sex (P=0,125). Age was also not significantly associated with survival (P=0,055), however, dogs with more than five years at the diagnosis showed a worse prognosis than dogs with less than five years.



Graph 12 – Survival of dogs with pulmonary oedema

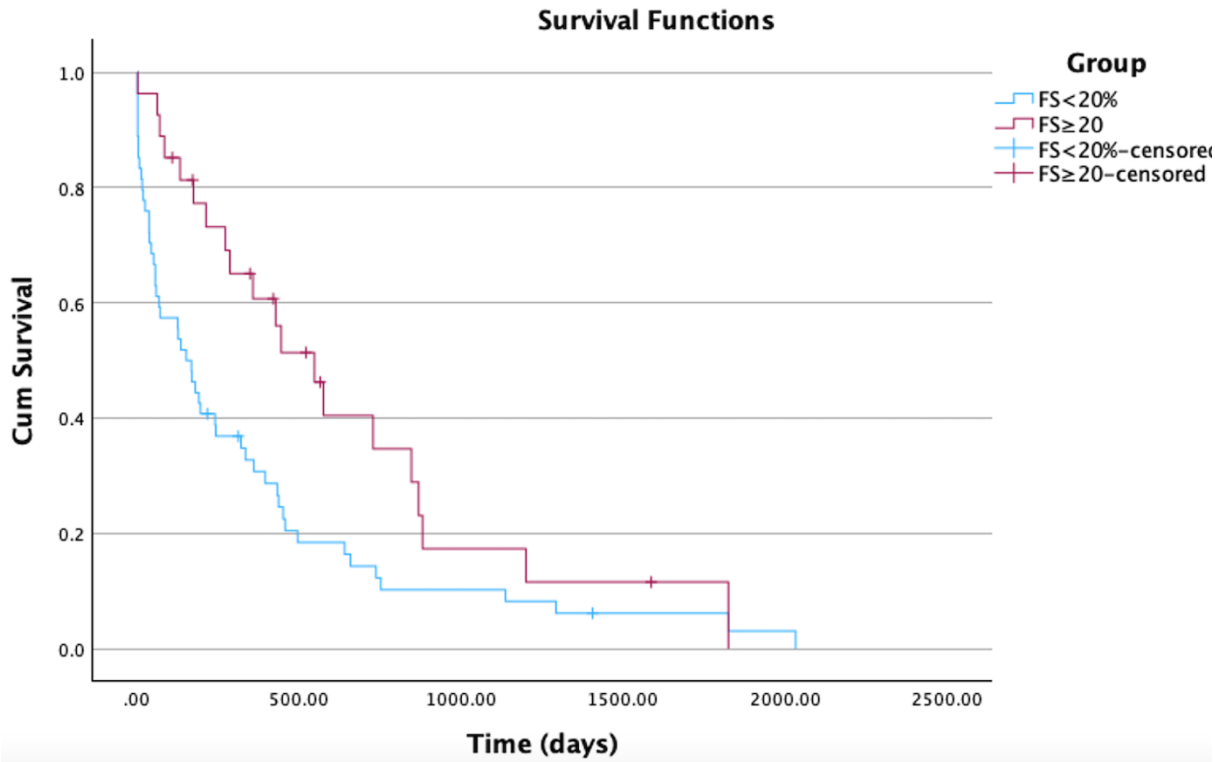


Graph 13 – Survival of dogs with dyspnea

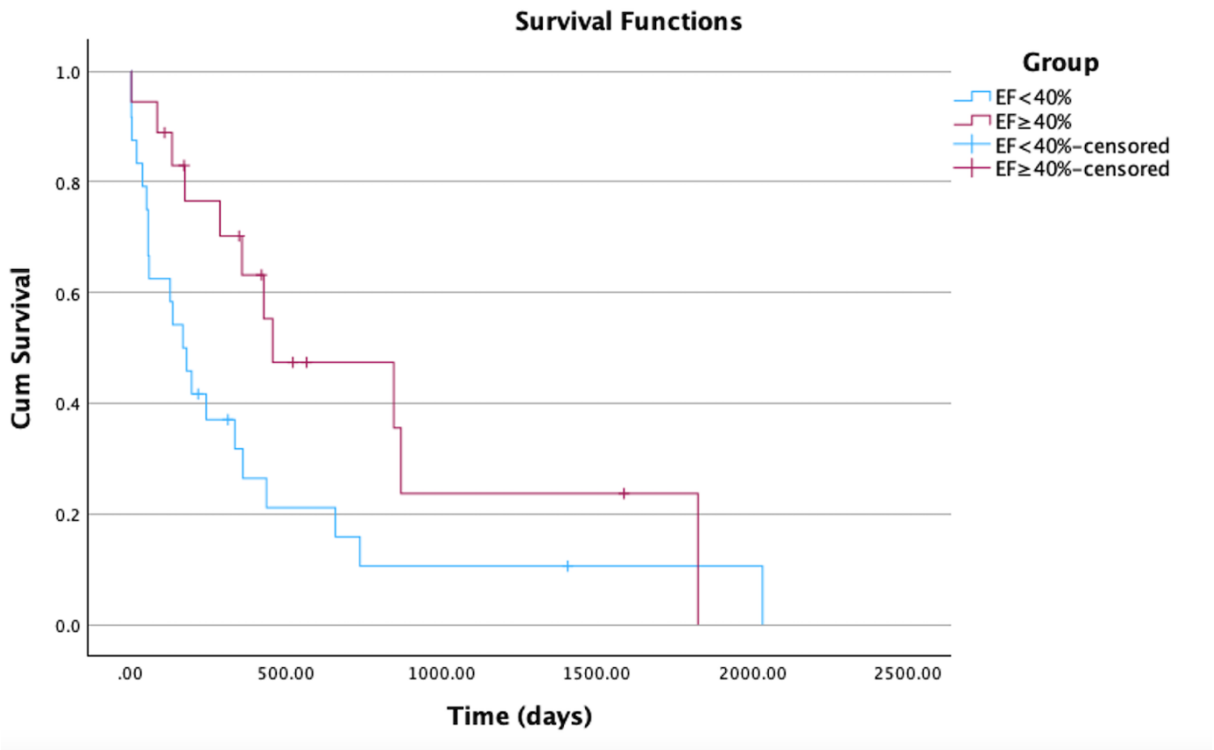


Graph 14 – Survival of dogs with ascites

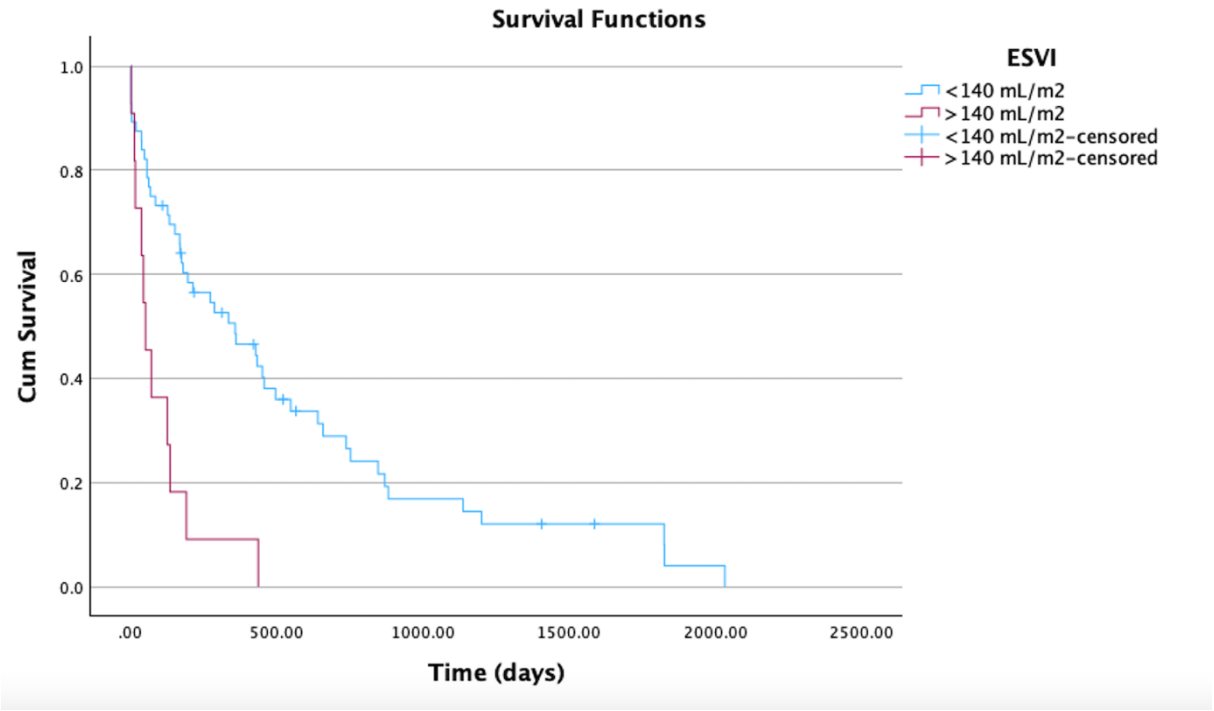
The echocardiographic parameters FS (P=0,018), EDVI (P=0,016), and ESVI (P<0,001) were demonstrated to be significant and negatively associated with survival. The EF measured by the Simpson method was not statistically significant, but when measured by the M-mode was statistically significant and negatively associated with survival (P=0,050).



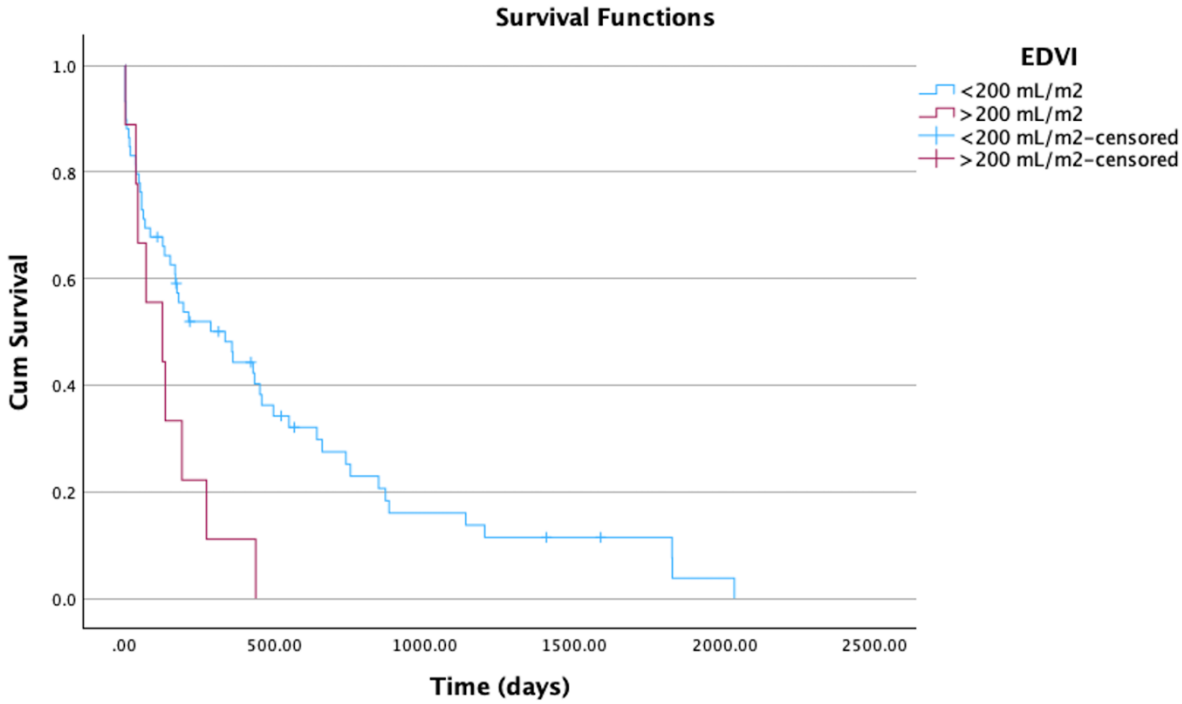
Graph 15 – Survival of dogs according to the FS value



Graph 16 – Survival of dogs according to the EF value



Graph 17 – Survival of dogs according to the ESV-I value



Graph 18 – Survival of dogs according to the EDV-I value

4 Discussion

In this dissertation, the author carried out a retrospective study of 163 dogs diagnosed with DCM, intending to compare it with studies done previously and characterize the disease in Portugal.

The most affected breeds in this study were Estrelas Mountain (20,9%), Boxers (17,8%) and Dobermanns (13,5%). In the study by Martin et al. (2009), Dobermanns (16%) and Boxers (14%) were also the breeds with the greatest prevalence. However, it should be noted that this prevalence varies according to the country where the study was performed. For example, the Doberman Pincher is the most affected breed in North America (O'Grady et al., 2009). The Great Dane was shown to be the most prevalent breed (46%) in Italy (Borgarelli et al., 2006) and in our study, this breed was the fourth most common (6,1%). In Sweden, has also been proved that Newfoundland is the most affected breed (Tidholm et al., 1997). Another retrospective study with 23 dogs with DCM in Portugal reported that one in every four dogs affected in this country is an Estrela Mountain dog (Luís & Carvalho, 1998), which follows this same study. Furthermore, NSB dogs represented 9,2% of the affected dogs with DCM and in the study made by Luís & Carvalho (1998), this percentage goes up to 26%. In that report, the author confirms that these dogs, despite being NSB, are animals of medium to large stature, probably crosses of predisposed breeds, being another local characteristic of the racial distribution of the disease in Portugal.

The average weight value of the dogs in this dissertation was 40,7 kg, which is similar to the average weight (37 kg) reported by Martin et al. (2009).

The vast majority of publications (Monnet et al., 1995;Calvert et al., 1997;Borgarelli et al., 2006) report a predominance of DCM in males, which is in line with the results obtained in this study. In previous publications, the published ratio was in general 2,7:1, 6:1 in Great Danes and GSDs, 5:1 in Dobermanns and Saint Bernards and 3:1 in Boxers, Golden Retrievers and Cocker Spaniels (Martin et al., 2009). In this study, similar results were identified with a general ratio of 2,8:1 and a ratio of 2,6:1 in boxers, though the ratio identified in Dobermans was 2,7:1. A study of Dalmatian dogs revealed that the disease only appeared in males (Freeman et al., 1996), as can be seen in this study (three male Dalmatian dogs). Despite the small number of specimens, it is worth noting that this also occurred in the study by Martin et al. (2009), in

which the four Dalmatian dogs under observation belonged to the male gender (Martin et al., 2009). However, few studies did not demonstrate a gender predisposition (Baumwart et al., 2005;Meurs et al., 2007). With this being said, despite both sexes carrying the DCM genotype, the males develop a more significantly congestive heart failure.

In the majority of the studies, the results concerning age follow those presented, since most dogs exhibit an age at diagnosis between six and eight years old (Monnet et al., 1995;Tidholm & Jonsson, 1997;Calvert et al., 1997;Martin et al., 2009). In this study, the mean age at diagnosis was 7 years, with the minimum age being 2 months in a boxer and 15 years in an NSB dog. These results are in agreement with the report made by Luís & Carvalho (1998), where the mean age of diagnosis was also 7 years and the youngest dog was 2 years and the oldest dog was 12 years. In our study, the age interval was a bit higher which reveals the diversity and greater number of dogs in this study. A retrospective study made with Boxers showed that the mean age at diagnosis on this breed was 6 years old, with a range from 1 to 11 years (Baumwart et al., 2005).

The symptomatology reported in previous studies include: depression, cough, loss of appetite (Tidholm & Jonsson, 1997), syncope, weight loss (Monnet et al., 1995) and exercise intolerance (Dukes-McEwan et al., 2003). The symptoms more present in this study were exercise intolerance (30,7%), lack of appetite (30,1%), dyspnea (25,8%), cough (21,5%) and syncope (7,4%), similar to Martin et al. (2009). In the study by Martin et al. (2009), 70% of the Boxers had episodes of collapse, 60% of the Golden Retrievers had a lack of appetite and in Great Danes, weakness was the most prevalent sign. An association between syncope and Boxers and Dobermans has also been reported in a few studies (Baumwart et al., 2005;Wess, 2022). Unfortunately, in our study, due to a lack of sufficient cases, it was not possible to prove the symptomatology in each breed. Sudden death is also frequently observed in Dobermans (O'Grady & O'Sullivan, 2004), but in this study due to a lack of information was not possible to analyze this clinical sign.

The clinical signs more prevalent in this study were ascites (20,8%), pulmonary edema (18,4%), cardiomegaly (15,9%) and pleural effusion (9,2%) and are not in agreement with the bibliographical references since the prevalence of pulmonary edema is between 73% and 97% (Monnet et al., 1995;Calvert et al., 1997;Borgarelli et al., 2006;Martin et al., 2009). In another study, Baumwart et al. (2005) reported a prevalence of pulmonary edema of 50% in Boxers. In the study by Martin et al. (2009), cardiomegaly was evidenced in 80% of cases. These

discrepancies between the results presented by us and those of reference are probably due to the high number of asymptomatic animals in our sample and, therefore, in the occult phase of the disease. Another explanation for this disparity is the fact that many dogs in our sample do not mention clinical signs.

The majority of the dogs (56%), were attributed to the most advanced stage of heart disease (stage C/D), which is in line with what is documented in other studies (Monnet et al., 1995;Borgarelli et al., 2006;Martin et al., 2009). The dogs in stage B1 corresponded to 11,5% and in stage B2 were 32,8%. All dogs in stage B are asymptomatic, although they can present syncope (Wess, 2022). Dogs in stage B1 only present arrhythmias and dogs in stage B2 can present both arrhythmias and LV systolic dysfunction with or without LV enlargement in diastole (Wess, 2022). However, in our study, there were many dogs (41), which the stage of the disease was not possible to be determined. Also, this is the first retrospective study, in our knowledge, that uses the Wess system (Wess, 2022) to classify the degree of heart failure. As such, it becomes impossible to make a statistically significant comparison between our study and the bibliography.

A murmur was detected in 23% of the population and similar values between 25% and 56% were reported in some studies (Monnet et al., 1995;Tidholm & Jonsson, 1997;Baumwart et al., 2005;Martin et al., 2009). However, a prevalence of over 76% is reported by Borgarelli et al. (2006). Despite, in our study, we had a small percentage of murmurs identified, compared to the bibliography, we cannot rule out the possibility that it was imperceptible upon auscultation since the presence of tachycardia, pulmonary edema, dyspnea, pleural effusion, among other alterations, can impair hearing.

The percentage of individuals with arrhythmias at the time of diagnosis (51,5%) was low when compared with the percentage of 89% presented by Martin et al. (2009). In our study, the percentage of dogs that had AF was 23% and VPCs was 20%, while the study by Martin et al. (2009) reported 45% of dogs with AF and 31% with VPCs, especially in Boxers and Dobermanns. However, it is important to take into account the high number of specimens of these latter breeds in the aforementioned study, which may explain the high incidence of AF and VPCs. In other studies, the percentage of VPCs is between 14 and 27%, and our result falls within this range (Monnet et al., 1995;Tidholm & Jonsson, 1997). The percentage of AF, in the various publications, is between 30 and 71%, especially in Irish Wolfhound, Great Dane, Newfoundland, German Shepherd and Saint Bernard (Monnet et al., 1995;Calvert et al.,

1997;Tidholm et al., 1997;Martin et al., 2009). In the base population under study, these breeds are represented by a reduced number of dogs, so it's not possible to make a comparison with other studies and this may be the reason why AF was not so much identified. Another reason we did not obtain a similar percentage may be due to the lack of Holter examinations since many arrhythmias are not detected when performing an in-house ECG, and/or it may be explained by the high number of asymptomatic cases. In our study, the breeds more affected were Estrela Mountain, Boxers and Dobermans, in which VPCs are more commonly seen (Dukes-McEwan et al., 2003). However, only 35% of Boxers exhibit VPCs, which does not match the 58% presented by Baumwart et al. (2005). SVPCs in our study were identified in one dog only (0,6%), not agreeing with the 9% observed by Martin et al. (2009). This can be explained by the lower amount of dogs in our study and by the fact that SVPCs are not so common. The 48,5% of individuals with sinus rhythm end up translating an abnormally high value when compared with 11% of Martin et al. (2009) and 20% of Tidholm & Jonsson (1997). This discrepancy may be due, once again, to the high number of asymptomatic animals and, therefore, in an early phase of the disease. The mean heart rate observed during the echocardiography test was 147 bpm and the mean heart rate of dogs in stage C/D was 163 bpm. It appears that the increase in heart rate is closely associated with a higher classification of heart failure, as was also found by Martin et al. (2009).

By carefully analyzing the results corresponding to the characterization of the different echocardiographic variables selected in the evaluation of DCM, we found that the base population is quite diverse with animals in different stages of the disease, which ultimately reflects reality. Because, if we selected only those that showed clear signs of the disease, we would be discarding animals that, despite being apparently healthy, already had the "occult" form of the disease.

The variables analyzed presented different distributions, reflecting variations in the symmetry of the data. Most variables demonstrated a positively asymmetric distribution, evidenced by the fact that the mean was higher than the median, suggesting the presence of high extreme values that shift the distribution to the right. On the other hand, variables such as Ao, LVIDd, LVIDs, RMVpeak and RTVpeak exhibited negative asymmetry, with the median slightly higher than the mean, indicating a greater concentration of values at the lower end of the distribution. Some variables, such as LVPWd, LA/Ao, SI and RTVpeakPG, presented little expressive asymmetry, approaching a symmetric distribution. These changes in symmetry

reflect the heterogeneity of the values obtained, possibly related to the individual characteristics of the patients and the variability inherent in the parameters evaluated.

Concerning these variables, it is important to mention some of the criteria used in estimating and analyzing them. It should be noted that in calculating ventricular volumes, the modified Simpson formula was chosen instead of the Teicholz formula. This is another formula capable of estimating ventricular volume and is applied based on the linear dimensions in the M-mode of the left ventricle, which may result in inaccuracies resulting from the geometric extrapolation required to convert a linear measurement into a three-dimensional volume. Another formula that is equally applicable in estimating these volumes is the area/length method. An experimental investigation by Lobo (2011) in Estrela Mountain, dogs did not reveal statistically significant differences between these last two methods.

During the echocardiographic assessment, the most critical parameters include the left ventricular dimensions during systole and diastole like LVIDd and LVIDs (Bonagura & Visser, 2022), the distance between the E wave peak and the interventricular septum (EPSS), the sphericity index (SI), fractional shortening (FS), and the ventricular ejection fraction (EF) (Dukes-McEwan et al., 2003). As a result, a diagnosis of DCM is established when the EDV-I exceeds 95 ml/m², the ESV-I surpasses 55 ml/m², the EPSS is greater than 6.5 mm, the SI is below 1.65, FS is less than 20%, and the EF is under 40% (Wess et al., 2017b). In the study, carried out by Lobo (2011) in Estrela Mountain dogs, he described that LVIDd values for male dogs greater than 59.6 mm and females greater than 58.9 mm are diagnostic indicators for DCM. In addition, he also proposes that LVIDs values greater than 41.8 mm can be a diagnostic measure. In our study, we discovered that 25 male Estrela Mountain dogs presented with an LVIDd mean of 66,7 mm, and seven female dogs presented with an LVIDd mean of 62,2 mm. We also verified that all 32 Estrela Mountain dogs in this study presented an LVIDs mean of 55,2 mm and only four dogs of this breed had LVIDs values below 41,8 mm. Consequently, our results follow the measures proposed by Lobo (2011). In our study, 63,6% of the dogs had an FS below 20%, 73,5% had an EF below 40%, 65,5% had an EDV-I greater than 95ml/m2, 64,5% had an ESV-I greater than 55 ml/m2, 95,2% had a SI lower than 1,65 and 82,7% showed to have an EPSS value greater than 6,5 mm.

In this study, the mean survival time was 335 days (48 weeks) and the median was 170 days (24 weeks), similar to Martin et al. (2009). The observed discrepancy suggests that the survival times do not follow a normal distribution. Consequently, the median survival time

serves as a more reliable measure of central tendency in this context. Furthermore, with the analysis of the results obtained by the Kaplan-Meier method, the percentage of dogs that were alive at one year of diagnosis with DCM was 30% and at two years was 14%, also very similar to the report by Martin et al. (2009), where survival rate at one year of disease was 28% and after two years was 14%. On the other hand, a study by Tidholm et al. (1997) reported a median survival time of 27 days (3-8 weeks) and a mean of 175 days (25 weeks), with a survival time of 17.5% after one year of the disease and 7.5% after two years. It is worth noting that in the study by Tidholm et al. (1997), 9% of the animals received ACE inhibitors; in the study by Martin et al. (2009), this percentage rose to 93%. Another report (Tidholm, 2006) documents a median of 126 days (18 weeks) and a survival time of 34% at one year with the disease and 20% at two years, also similar to our results. Another report by Monnet et al. (1995) revealed a median of 65 days, with 37.5% at one year with DCM and 28% at two years, in which 37% of dogs received an ACE inhibitor. Also, a study by Borgarelli et al. (2006) published a median of 671 days, being the highest value that has been published to date, and as such, it is hard to explain. One of the possible justifications is related to the inclusion of asymptomatic or moderately symptomatic animals. In the Monnet study discussed above, the authors suggest that canines that survive at least seven months have a high probability of becoming long-term survivors, with some cases reaching forty months (Monnet et al., 1995). In our study, analysis of the survival curve reveals that after two and a half years (913 days), there is a good probability of long-term survival since the decrease in the proportion of living dogs slows abruptly. Regarding the estimated survival time in the different breeds, Dobermanns presented a lower median (95 days) compared to Boxers (216 days) and Estrela Mountain Dogs (202 days), whose presence of a significant number of Estrela Mountain Dogs in the occult phase explains the proximity of the values obtained with those published by Lobo (2011), since in this study the sample also included animals in the initial phase of the disease.

The existence of breeds with different histological forms also contributes to these final results. It is also worth highlighting the influence of treatment on the estimation of this period since otherwise, the disparity in values would probably be greater. Although asymptomatic individuals were not subject to any type of treatment, the same was not true for symptomatic individuals, whose therapy consisted of the administration of an ACE inhibitor, furosemide, pimobendan, and an antiarrhythmic when indicated (digoxin, diltiazem and/or amiodarone). The treatment regimen was deliberately not included in this review since the main objective

was related to the diagnostic and prognostic criteria. The treatment instituted for all animals was standardized, always being applied by the same veterinarian.

As previously mentioned in the results, only 39% of the animals, which was possible to follow up, were euthanized due to cardiac reasons, with the remaining euthanasias being motivated by other diseases. Also, in total, 50% of the animals were euthanased, which is very similar to the 51% obtained by Martin et al. (2009). These values are low when compared to the other two studies, where the range of euthanasia goes between 74 and 84% (Tidholm & Jonsson, 1997;Tidholm, 2006). The greater or lesser percentage of this practice may be related to the financial conditions and ethical thinking of the owners. In 1997, euthanasia was reported in about half of the Dobermans, the rest dying naturally, and of these, 20% died suddenly within the first three months (Calvert et al., 1997). In 2002, Petric published that 33% of Dobermanns died from CHF, 29% from euthanasia, and 33% from sudden death (Petric et al., 2002). In our study, natural death occurred in 50% of dogs, similar to Martin et al. (2009), where they died due to CHF, sudden death, or another disease. On the other hand, a study by Borgarelli et al. (2006) showed that only 39,7% of the dogs died of cardiac causes, with 3,2% of these being euthanized and 23,8% with sudden death, although 50.8% of the individuals remained alive until the end of the study. In contrast, our study presented 89,1% of the dog's death due to cardiac reasons, with 43,9% being euthanized. Comparing all the information presented, it is easy to see that the percentage of euthanasia does not follow a pattern, which denotes the subjective nature of this act, as the reasons can vary significantly depending on the principles, cultures and economy of the owners.

DCM can lead to two cardiac outcomes, namely, sudden death or natural death due to CHF. These can be accompanied by different prognostic indicators. In this case, indices related to ventricular ectopy help to estimate the occurrence of sudden death, on the other hand, cardiac function indices can help to predict death of cardiac origin (non-sudden). In this retrospective study, it was not feasible to accurately ascertain whether the cause of death for each dog was sudden or otherwise.

Some studies have been conducted to characterize prognostic indicators in dogs with DCM. The presence of pulmonary edema, pleural effusion (Monnet et al., 1995), age, dyspnea, ascites (Tidholm & Jonsson, 1997), AF and bilateral heart failure (Calvert et al., 1997) end up representing independent parameters related to short survival times.

According to the study by Borgarelli et al. (2006), parameters such as age and dyspnea did not influence the survival rate. Ascites was shown to be a useful prognostic indicator, however, its manifestation did not have any effect on the survival rate in dogs with a restrictive pattern. This author also showed that the classification of dogs according to the stage of CHF can be a measure of prognosis in dogs with DCM (Borgarelli et al., 2006).

In our work, clinical signs such as pulmonary edema, dyspnea and ascites prove to be significant prognostic indicators, being significantly and negatively associated with survival. Also, pleural effusion was shown to be negatively associated with survival, however, our results didn´t show to be significant. In the study by Monnet et al. (1995), this parameter was the most significant prognostic indicator. Borgarelli et al., 2006, on the other hand, suggest the restrictive pattern as the most relevant negative prognostic indicator. However, the database collected in this study was not sufficient to confirm this relevance since only twenty-two cases showed a restrictive pattern and thirty-one a non-restrictive pattern, and we do not have any information on the remainder. The variable breed did not show to be a relevant prognostic indicator in our study, as well as in the study by Monnet et al. (1995). However, in two reports, the Doberman Pincher breed was considered a negative prognostic indicator (Calvert et al., 1997;Martin et al., 2010). VPCs were not an independent prognostic indicator both in our study and in Monnet et al. (1995), although in the report by Martin et al. (2010), this was negatively and significantly associated with survival. AF was considered a negative and significant prognostic indicator in a study with Doberman Pinchers (Calvert et al., 1997), but both in our study and in Borgarelli et al. (2006) dogs without AF tended to have longer survival times compared to those with AF, though this difference was not statistically significant. In the study by Martin et al. (2010), on the contrary, the presence of AF was significantly and positively associated with survival. The variable sex was demonstrated to be a promising prognostic indicator in our study, with male dogs having a worse prognosis compared to females. However, this variable was not significantly associated with survival. The Wess staging method for congestive heart failure (CHF) demonstrated its utility as a significant negative prognostic indicator in this study. Dogs classified in stage C exhibited a markedly poorer prognosis than those in stages B2 and B1. Similarly, the ISACHC classification has been identified as a significant negative prognostic factor in previous research, with higher ISACHC classes being strongly associated with reduced survival (Martin et al., 2010). Furthermore, another study reported biventricular CHF as a significant negative predictor of survival (Calvert et al., 1997). The variable age was negatively but not significantly associated with survival in our study. Older dogs (more or equal to five

years) showed a worse prognosis compared to younger dogs (less than five years), which allows us to conclude that the later the diagnosis, the worse the prognosis. This result can be explained by the fact that at these older ages, the disease is at a more advanced stage, possibly because it was not diagnosed in the animal while it was young and because the survival time is naturally shorter, as animals in a higher age range live less time. In the study by Tidholm et al. (1997), on the contrary, dogs less than five years old had poorer survival than those greater than five years, which goes against our results. Other two reports did not show an association between age and survival (Monnet et al., 1995;Borgarelli et al., 2006) although the study by Martin et al. (2010) proved that older dogs had an increased risk of survival.

According to our analysis, the echocardiographic parameters useful in estimating survival time include FS, EF, EPSS, EDV-I and ESV-I. The authors Monnet et al. (1995) and Tidholm et al. (1997) did not find any association between echocardiographic parameters and survival. Another report by Martin et al. (2010) showed that the left ventricular diameter index was a significant and negative prognostic parameter.

In our study, we analyzed the EF parameter measured by the Simpson method (B-mode ultrasonography) and by the M-mode. The results showed that both methods demonstrated a negative association with survival. However, the EF measure by the Simpson method was not significantly associated with survival, unlike the EF measure by the M-mode, which was revealed to be a significant prognostic indicator. On the contrary, Borgarelli et al. (2006) showed that EF measured by the Simpson method was a significant and negative prognostic indicator. Another echocardiographic parameter that proved to be significantly and negatively associated with survival was the FS, where dogs with a percentage of FS less than 20% showed a poorer prognosis than dogs with an FS value greater or equal to 20%. However, in the study by Borgarelli et al. (2006), FS did not show any association with survival. According to the author above, animals with DCM have not only systolic dysfunction but also ventricular dyskinesia, and in the presence of mitral insufficiency, the FS value may appear to increase due to septal movement. As such, the ejection fraction via 2D mode appears to represent a more reliable index of global myocardial function than the FS (Borgarelli et al., 2006). In our study, the parameter EPSS was negatively associated with survival in dogs with an EPSS value greater than 6,5 mm, although this parameter was not statistically significant, as well as in the study by Borgarelli et al. (2006). In other two studies (Monnet et al., 1995;Tidholm et al., 1997), both a decrease in FS and an increase in EPSS values showed no

association with longevity, despite this parameters being useful in the diagnosis of DCM. The ESV-I was the most significant and negative echocardiographic parameter associated with survival, with dogs with an ESV-I value greater than 140 ml/m^2 having a substantially poor prognosis compared with dogs with ESV-I values less than 140ml/m^2. This parameter was also expressed in the study by Borgarelli et al. (2006) and proved to be a significant and negative prognostic indicator. Finally, the EDV-I was also demonstrated to be significantly and negatively associated with survival since dogs that present an EDV-I value greater than 200 ml/m^2 live much less time, compared with dogs that had an EDV-I less than 200 ml/m^2. To our knowledge, this last parameter was not studied as a possible prognostic indicator in other retrospective studies, so further investigation is recommended.

5 Conclusions

In conclusion, the results of this study are generally in agreement with those published, except for a few points, which are duly justified. It is important to note that despite the great diversity of studies carried out in this area, comparisons between them end up being erroneous, as it is difficult to compare results from different techniques, conditions and methods. After all this analysis, it is worth reinforcing that the predisposed breeds in Portugal include Estrela Mountain Dogs, Boxers and Dobermanns; it is a disease that mainly affects large animals; the male gender is the most prevalent, with a male-to-female ratio of 2,8:1; the average age at diagnosis is 6-8 years, and it can affect any age; the characteristic but not pathognomonic symptoms include exercise intolerance, lack of appetite, dyspnea, murmur, cough and syncope; visible radiographic changes include pleural effusion, pulmonary edema, and cardiomegaly; the most prominent arrhythmias include AF and VPCs; the variables FS, EF, EDV-I, ESV-I, EPSS, and SI proved to be useful diagnostic parameters; it is a disease accompanied by high mortality, as there is a sharp drop in the number of survivors in the first few days after diagnosis, suffering a reduction to 79,8% in the first 15 days; the median survival value was 170 days; dogs in a more advanced stage of the disease, according to the Wess classification, show a worse prognosis and the best prognostic parameters in our study were pulmonary edema, dyspnea, ascites, EF, FS, EDV-I and ESV-I.

Most of the stipulated objectives were successfully achieved however, there were many limitations, such as the lack of post-mortem confirmation of diagnosis and histological evaluation. Some patients were under the effect of previous therapy at the time of the echocardiographic examination, which ended up influencing the measurements at the time of diagnosis.

The levels of plasma taurine and carnitine were not also measured and the fact that there were no reference echocardiographic and electrocardiographic values for all the breeds under study made our analysis difficult.

The lack of follow-up and periodic monitoring after diagnosis of some of the animals under study, the absence of previous cardiovascular examinations and the lack of information ended up limiting the knowledge about the natural history of the development of DCM in the different breeds, not allowing the use of more diagnostic parameters, such as the myocardial performance index and tissue Doppler measurement. Another limitation is the absence of a control group, the presence of tachycardia, which ends up influencing many of the parameters

mentioned here, such as measurements in the LV and peak velocities at the level of transmitral flow; the lack of measurement of blood pressure and the lack of analysis of the influence of medical treatment on survival time. Although euthanasia was performed on individuals with manifestations of severe CHF, it ended up influencing the estimate of survival time to some extent. The fact that hypothyroidism was not detected in all animals in the study is another limitation to mention, as these tests were only performed on individuals with clinical suspicion of the disease.

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