The Longitudinal Outcome Of Canine (K9) myxomatous mitral valve disease (LOOK-Mitral registry): Baseline characteristics

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Abstract
Introduction: The Longitudinal Outcome Of Canine (K9) myxomatous mitral valve disease (MMVD) registry (LOOK-Mitral registry) was established to de- scribe the natural history and predictors of outcome in dogs affected by MMVD. This study was intended to describe the baseline characteristics of dogs in the LOOK- mitral registry.
Animals: Dogs with echocardiographic evidence of MMVD were prospectively enrolled by thirteen referral centers.
Results: A total of 6102 dogs with MMVD were included. The median age was 10 years (1e19 years), and mixed breed was the most common breed (n 1⁄4 1,360, 22%). Concomitant diseases were reported in 2459 dogs with chronic respiratory dis- eases occurring most frequently (14%), followed by the presence of azotemia (6%) and orthopedic diseases (5%). Regarding disease severity, 65% of dogs were in ACVIM Stage-B1, 15% in Stage-B2, and 20% in Stage-C. Dogs in Stage-B1 were younger ($p<0.001$) than dogs in other stages. Murmur intensity, heart rate during physical examination, and radiographic vertebral heart score were positively associated with the stage. Dogs in Stage-C were more likely to have tachypnea ($p<0.001$), dys- pnea ($p<0.001$), cough ($p<0.001$), syncopal episodes ($p<0.001$), and tachyarrhyth- mias ($p<0.001$) compared to dogs in Stage-B1 and B2. Echocardiographic indices of left atrial and ventricular size were positively correlated with the ACVIM stage. In- terestingly, 4% of dogs that weighed <20 kg had an increased normalized end- systolic left ventricle internal diameter (>1.26).
Conclusions: This study contributes to a better understanding of the clinical characteristics of dogs affected by MMVD and provides new findings that may be of clinical relevance.

Introduction
Myxomatous mitral valve disease (MMVD) is the most common heart disease in dogs; however, prospectively acquired data describing the natural history and prognostic factors in a large population of dogs affected by this disease are sparse [1].
In human medicine, patient registries have become an accepted way to prospectively collect large amounts of data on specific disease processes. In general, patient registries, or more specifically disease registries, can be defined as organized systems that collect information to describe the natural history or to evaluate specific outcomes of a population affected by a specific disease [2]. The primary limitations associated with the use of registries are the absence of a priori testing hypotheses, the higher risk of bias, and loss of follow-up [2,3]. However, despite these limitations, the use of patient registries in human medicine has increased in recent decades due to their ability to provide useful information that is generalizable to a real- world practice setting and their lack of some limitations of randomized controlled trials such as size, cost, time, or the presence of rigid inclusion and exclusion criteria [2]. The Longitudinal Outcome Of Canine (K9) myxomatous mitral valve disease registry (LOOK-Mitral registry) was established with the main purpose of prospectively collecting clinical and diagnostic data from a large population of dogs affected by MMVD. Because we studied a relatively unselected population compared to those enrolled in clinical trials, our data may provide a better clinical description of canine MMVD as encountered in a real-world practice setting. This study aims to describe the baseline clinical and diagnostic characteristics of dogs enrolled in the LOOK-Mitral registry.

Materials and methods

This is a prospective multicenter observational study. Dogs were enrolled from 1st November 2015 to 31st October 2018 by 13 veterinary cardiology specialty servicesg involved in the LOOK-Mitral registry project. Follow-up information will be collected until 31st October 2021 or until patients' death.

Methods

Among all dogs referred to the 13 veterinary cardiology services during the three-year study period, dogs with echocardiographic evidence of MMVD were included, regardless of the reason for referral. Dogs were subsequently classified with respect to the ACVIM stages of MMVD: Stage-B1 was defined by the absence of echocardiographic enlargement of the left atrium (LA) and left ventricle [4]. Stage-B2 was defined by MMVD associated with echocardiographic evidence of both LA and left ventricular enlargement (left atrium to aortic ratio (LA:Ao) ! 1.6 and left ventricular internal diameter normalized in diastole (LVIDd_N) ! 1.7), but the absence of current or historical clinical signs of congestive heart failure (CHF). Stage-C was defined by the presence of current or past clinical signs and/or radiographic evidence of CHF. Clinical signs of CHF were defined as tachypnea, dyspnea, and/or cough that resolved by normalization of the resting respiratory rate (RR) and respiratory efforts with medical treatment with furosemide, together with any combination of pimobendan, an angiotensin- converting enzyme inhibitor, or spironolactone. Moreover, dogs in which furosemide was pre- scribed by the specialist based on clinical and echocardiographic findings were also included in ACVIM Stage-C. Since the identification of patients in refractory CHF is challenging in clinical practice and considering that this would likely represent a very small group of dogs with advanced disease, no further classification was made among dogs with current or past clinical signs of CHF.

The echocardiographic diagnosis of MMVD was based on the presence of thick and/or prolapsing mitral valve leaflets on two-dimensional (2D) echocardiography and mitral regurgitation (MR) identified using color Doppler imaging. Mitral valve prolapse was identified when there was protrusion of one or more leaflet scallops dorsal to the annular plane, and this phenomenon was evident in more than one echocardiographic view [5]. The presence of MR was assessed using color Doppler and defined by a jet or jets that were evident during every visualized cardiac cycle. Data were entered into a database at the time of enrollment as well as at scheduled and unscheduled recheck evaluations. At the time of enrollment, all dogs underwent a physical and echocardiographic examination. Any additional test was performed at the discretion of the cardiologist. Data describing signalment and patient history included breed, age, sex, body weight (BW), the presence of cough, history of syncopal episodes, and resting RR at home. The following physical examination findings were retrieved from the database: the presence/absence of abdominal effusion, RR, the presence and intensity of murmur, heart rate, and systolic blood pressure. Tachypnea was defined as a resting RR greater than 36 breaths per minute, while dyspnea was defined by the appearance of difficult or labored breathing. Murmurs were classified as soft, moderate, loud, or palpable using a four-level grading scheme [6]. When assessed, systolic blood pressure was measured non-invasively with Doppler sphygmomanometry as previously reported [7].

At the time of enrollment, a standard echocardiographic examination was performed in all dogs by a board-certified cardiologist or by a cardiology resident supervised by a cardiologist. All measurements were obtained by the examiner at, or shortly after, the conclusion of the echocardiographic assessment. The 2D LA:Ao was calculated from measurements obtained from the right parasternal short-axis view, using one of the two methods previously reported [8,9];

the choice of method was at the discretion of the cardiologist. The end-diastolic and end-systolic left ventricular chamber dimensions were obtained from M-mode images guided by a right parasternal short-axis view at the level of the papillary muscles. These dimensions were indexed to body size, providing the LVIDd_N and the normalized left ventricle internal diameter at the end of systole (LVIDs_N) [10,11]. Pulsed-wave spectral Doppler was used to obtain the peak velocity of early diastolic transmitral flow with the sample volume placed at the tips of the mitral valve leaflets in the left apical four-chamber view. The presence or absence of tricuspid regurgitation (TR) was assessed by color Doppler, and when present, the TR peak velocity was obtained by continuous-wave spectral Doppler.

Left atrial enlargement was defined by a LA:Ao 1.6. In order to investigate the association between the degree of LA enlargement and some of the clinical findings and radiographic variables, dogs with LA enlargement were further arbitrarily divided into dogs with mild to moderate LA enlargement (LA:Ao 1.6 and < 2) and dogs with severe LA enlargement (LA:Ao ! 2). Left ventricular enlargement was defined by an LVIDd_N 1.7 as suggested by the ACVIM guide-lines [4]. End-systolic left ventricular dimension scaled to body size served as an index of systolic myocardial function; dogs in which this value exceeded the published 97.5th percentile (1.26) were considered to have systolic myocardial dys- function [11]. Pulmonary hypertension (PH) was defined by a TR peak velocity > 3.0 m/s [12]. Given the prognostic usefulness of estimated pulmonary arterial pressure (ePAP) > 55 mmHg, we further divided patients with PH into those with an ePAP > 55 mmHg and those with an ePAP 55 mmHg [13].

If thoracic radiography was performed up to 30 days before the enrollment, the presence/absence of CHF, vertebral heart score (VHS), as well as the presence of other concomitant thoracic abnormalities were determined [14]. Dogs were consid- ered to have radiographic evidence of CHF only when radiographs were available for interpretation by a cardiologist or a radiologist at the time of the examination. The presence of LA enlargement in conjunction with a typical distribution of pulmonary opacities was required for a radiographic diagnosis of CHF. If VHS was not reported in the original medical record and radio- graphs were available for review, this was calculated by a single operator (AF). Cardiomegaly was identified when the VHS was greater than 10.5 or above the specific breed upper limit when avail- able [15e19].

Arrhythmias were diagnosed based on a standard six-lead electrocardiogram (ECG) or based on the ECG trace recorded during the echocardiographic examination. If ECG findings were not included in the medical record, it was assumed that the dog did not have arrhythmias.

The diagnosis of concomitant diseases was based on the review of medical records, blood tests, and other diagnostics tests when available. If the medical record did not report concomitant diseases or if the review of the available

laboratory data and/or findings of other diagnostic tests did not suggest the presence of clinically significant concomitant disease, the dog was considered to be affected only by MMVD.

Statistical analysis

Statistical analyses were performed using dedicated computer software. The distribution of continuous variables was assessed by visual inspection of normal quantile plots. All continuous variables in our study were not normally dis- tributed and, therefore, are all presented as median and range (minemax). Count and per- centage are used for categorical variables.

Continuous variables were compared using the KruskaleWallis test. If the omnibus test revealed a significant difference, the SteeleDwass test was used. Associations between

categorical variables were evaluated using the Pearson's Chi-squared test of independence and Bonferroni-adjusted p- values. Alpha was set to 0.05.
For murmur intensity, pairs of murmur categories were compared between stages (Soft vs. Moderate, Moderate vs. Loud, and Loud vs. Palpable).

Results

In the LOOK-Mitral registry, 6102 dogs were enrolled. The 20 most common breeds, out of the 190 represented, are reported in Table 1. At the time of enrollment, Cavalier King Charles Spaniels (CKCSs) were younger than other most common breeds (Fig. 1). Moreover, when only dogs in ACVIM Stage-C were considered, CKCSs were younger (median age: 9 years, range: 6e13 years) than some of the other most common breeds (Fig. 2).
In 86 dogs that had not experienced current or past clinical signs of CHF, the LA:Ao ratio (n 1⁄4 50) or LVIDd_N (n 1⁄4 36) was not available for review. Therefore, 6016 of the 6102 dogs were subsequently classified into three stages. There were 3891 dogs in Stage-B1 (65%), 889 in Stage-B2 (15%), and 1236 in Stage-C (20%). Summary statistics, including comparisons of signalment, clinical signs, and physical examination findings between stages are reported in Table 2 a/e/c. An association between the age and the stage of the disease was found with dogs in Stage-B1 being younger and dogs in Stage-C being older when compared with dogs in other stages (Fig. 3). Concerning BW, dogs in Stage-B1 weighed more ($p<0.001$) than dogs in Stage-B2 and Stage-C. No difference in sex distribution among stages was found (p1⁄40.19).
Based on the RR at home, tachypnea or dyspnea were reported in 2% (n 1⁄4 75) of dogs in Stage-B1, 1% (n 1⁄4 10) of dogs in Stage-B2, and 27% (n 1⁄4 343) of dogs in Stage-C. The same clinical signs were reported in 4% (n 1⁄4 176) of dogs in Stage-B1, 8% of dogs in Stage-B2 (n 1⁄4 69), and 40% of dogs in Stage- C (n 1⁄4 495) based on RR during the physical examination. Based on both RR during the physical examination and RR at home, dogs in Stage-C more often had tachypnea ($p<0.001$) and dyspnea ($p<0.001$), compared with dogs in other stages. The presence of cough and the presence of syn- copal episodes were positively associated with the stage of the disease (Table 2). Moreover, in dogs
without radiographic evidence of pulmonary edema and without concomitant respiratory disease, cough was more likely to occur in dogs with severe LA enlargement ($p<0.001$) than in dogs with mild to moderate LA enlargement, regardless of the stage of MMVD (Fig. 4). Out of the 369 dogs with PH, 220 (60%) had an ePAP > 55 mmHg. The presence of syncopal episodes was associated with the presence of PH in both dogs with an ePAP >55 mmHg ($p<0.001$) and 55 mmHg ($p<0.001$), whether or not a concomitant chronic respiratory disease was reported.
The intensity of the murmur was positively associated with the stage of disease and with the degree of LA enlargement (Fig. 5). In particular, dogs in Stage-B1 were more likely to have a soft or moderate murmur (69%, n 1⁄4 2525), while dogs in Stage-B2 and Stage-C were more likely to have a loud or palpable murmur, accounting respectively for 78% (n1⁄4692) and 89% (n1⁄41094) ofthemurmurs detected in these stages. Moreover, dogs in Stage-B1 were more likely to lack a murmur when compared to dogs in other stages ($p<0.001$). In fact, in 6% of dogs in Stage-B1 (n 1⁄4 215), but only in 0.3%(n1⁄42)ofdogsinStage-B2andin0.3%(n1⁄43) of dogs in Stage-C, murmurs were not recorded. The majority of dogs with any degree of LA enlargement had loud or palpable heart murmurs, while 3% (n 1⁄4 39) of dogs with mild to moderate LA enlargement and 2% (n 1⁄4 17) of dogs with severe LA enlargement had soft murmurs. Conversely, in dogs
with normal echocardiographic LA dimensions, 37% (n 1⁄4 1324) had moderate murmurs, 26% (n 1⁄4 935) had loud murmurs, and 5% (n 1⁄4 178) had palpable murmurs. A positive association was found between the stage of disease and HR detected during the physical examination (Fig. 6).

Electrocardiographic data and comparisons among stages are summarized in Table 3. In addition to the ECG trace recorded during echo- cardiography, a six-lead ECG was obtained for 565 dogs (9%). Arrhythmias were identified in 584 dogs (9%). The prevalence of sinus arrhythmia was negatively associated with the stage of the disease (Table 3). Rhythm disorders were more common in dogs in Stage-C with atrial premature complexes (APCs) ($p<0.001$), supraventricular tachycardia ($p<0.001$), and atrial fibrillation (AF) ($p<0.001$) being more common in dogs in this stage, when compared with dogs in other stages. Dogs in Stage- B2 were more likely to have APCs (p1⁄40.025) and AF (p1⁄40.046) when compared with dogs in Stage-B1. Dogs with AF (p1⁄40.86), ventricular (p1⁄40.23) and supraventricular tachycardia (p1⁄40.08), second and third-degree atrioventricular block (p1⁄40.61), or sick sinus syndrome (p1⁄40.68) were not more likely to have syncopal episodes than dogs without these arrhythmias.
Thoracic radiographs of 1666 (28%) dogs were obtained. Baseline characteristics concerning thoracic radiographic variables and comparisons among stages are summarized in Table 4. The VHS was positively associated with the stage of the disease. Cardiomegaly was radiographically detected in 117 dogs (33%) with a normal LA:Ao and LVIDd_N. Moreover, 21% (n 1⁄4 46) of the dogs with echocardiographic mild to moderate LA enlarge- ment and an LVIDd_N ! 1.7 and 14% (n 1⁄4 44) of dogs with severe LA enlargement and an LVIDd_N ! 1.7 had a normal VHS.
Baseline echocardiographic data and comparisons between stages are summarized in Table 5. Echocardiographic indices of size and function were respectively correlated, positively and neg- atively, with the stage of the disease. Systolic dysfunction was identified in 5% of the dogs (n 1⁄4 331): 59 dogs in Stage-B1 (1.5%), 75 in Stage- B2 (8%), and 197 in Stage-C (16%). Systolic myo- cardial dysfunction was present in 12% (n 1⁄4 89) of the dogs with a BW 20 kg. When these dogs were excluded, only 240 (4%) with a BW < 20 kg had evidence of systolic dysfunction: 28 dogs were in Stage B1 (1%), 60 dogs were in Stage-B2 (7%), and 152 in Stage-C (14%).
Tricuspid regurgitation was present, and the peak velocity was measurable in 72% of the dogs (n 1⁄4 4392), and 36% (n 1⁄4 1567) of those had evidence of PH. An ePAP >55 mmHg was reported in 6% (n 1⁄4 385) of the total population and in 25% of dogs with PH.
The prevalence of PH was positively associated with the stage of the disease independently from the concomitant presence of respiratory diseases (Table 5). Moreover, dogs in Stage-C were more likely to have an ePAP >55 mmHg than dogs in Stage-B2 ($p<0.001$) and dogs in Stage-B2 than dogs in Stage-B1 ($p<0.001$). The presence of abdominal effusion detected during the physical examination was positively associated with an ePAP >55 mmHg ($p<0.001$).
Data describing concomitant diseases are sum- marized in Table 6. Concomitant diseases were present in 2459 dogs (41%). Dogs in Stage B1 ($p<0.001$) and Stage B2 (p1⁄40.003) were more likely to present with concomitant diseases than dogs in Stage-C. Chronic respiratory disease and azotemia were the two most common comorbidities in dogs in Stage-B1 and Stage-C, while chronic respiratory disease and neurologic disease and neurologic signs, in particular, intervertebral disk disease (n 1⁄4 120, 13%) and seizures (n 1⁄4 100, 11%), were the most common comorbidities reported in dogs in Stage-B2 in our population.

Discussion

We described the baseline characteristics of a large population of dogs affected by MMVD enrol- led in the LOOK-Mitral registry. To the author's knowledge, this is the first time that a disease registry has been used to prospectively collect data in a population of dogs affected by MMVD.
MMVD is an age-dependent disease that more commonly affects small to medium-sized, middle- aged to geriatric dogs. In this study, mixed breed dogs were the most common breed,

followed by CKCS and Chihuahua, as previously reported [20,21]. While some purebred dogs, like the CKCSs, have been reported to have a higher prevalence of MMVD, the finding that small, mixed breed dogs represent the most common breed in our study
might simply reflect the fact that small, mixed breed dogs are probably overrepresented in the general canine population rather than a predisposition for mixed breed to develop MMVD. More- over, designer dogs, which are not recognized as purebred, are frequently obtained by crossing breeds commonly affected by MMVD, such as CKCS and poodle. Therefore, this may also explain the high prevalence of MMVD in mixed breed dogs in our population.

An early onset of the disease has been reported in CKCSs, and our results are in agreement with what was previously reported [22]. This may reflect that owners and referring veterinarians are aware of the high prevalence of MMVD in this breed and are more likely to refer these dogs earlier to specialists. However, when only dogs in Stage-C were considered, CKCSs were younger when com- pared with some of the other 20 most common breeds in our study. This might suggest that CKCSs might develop CHF at a younger age. The association between age and the stage of disease found in this study confirms what has already been reported, and it is not surprising considering that MMVD is a slowly progressive, age-dependent dis- ease [23].

In this study, a relatively high number of patients in Stage-B2 presented with tachypnea/ dyspnea and/or cough. While these clinical signs are commonly reported in dogs with CHF, they are not specific for this condition and can be caused by other diseases. Our results suggest that treatment decisions should not be based solely on these findings but based on a complete diagnostic assessment. However, because thoracic radio- graphs were not performed in all dogs with clinical signs, it is possible that some of the dogs classified as Stage-B2 were actually in CHF.

Our results showed an association between the presence of cough and the degree of LA enlarge- ment in dogs that did not have radiographic evi- dence of pulmonary edema or evidence of concomitant respiratory disease, regardless of the ACVIM stage. Two previous studies have found an association between LA enlargement and cough, and the mechanism was assumed to be com- pression of the mainstem bronchi caused by the enlargement of the LA [24,25]. The majority of the dogs in these studies were elderly, small-medium- sized breeds that are known to be predisposed to bronchomalacia, and therefore, they are more likely to have bronchial collapse as a consequence of the LA enlargement [24,25]. However, a previous study failed to find an association between LA enlargement and airway collapse in dogs with MMVD [26].

Syncopal episodes were identified in 369 dogs, which accounted for 6% of our population. Both bradyarrhythmia and tachyarrhythmias, as well as PH and the presence of pulmonary edema, have been reported as cardiac causes of syncope [27]. In our study, similar to what was previously reported, PH has been identified as a possible cause of syncope in dogs with MMVD [20]. The prevalence of PH in our population was 36%, and 6% of our dogs had an ePAP >55 mmHg. Previous studies have repor- ted a prevalence of PH between 14% and 53%, depending on the cut-off value of TR velocity used to establish the presence of PH and on the severity of the MMVD [13,28,29]. While dogs with MMVD might develop PH for different reasons, the most common cause, particularly in dogs in Stage-C, is thought to be a passive increase in pulmonary venous pressures due to increased LA pressure (after capillary PH) [30]. Chronic elevation in LA pressure may induce pulmonary vascular remodeling, vasoconstriction, and an increase in pulmo- nary resistance [31]. Therefore, it is not surprising
that 58% of dogs in Stage-C had PH and 39% had an ePAP >55 mmHg.

An association between the presence of synco- pal episodes and different types of arrhythmias was not found in our study. This is in agreement with a previous study in which 24-h Holter mon-

itoring failed to find an association between syncopal episodes and arrhythmias in dogs with MMVD [32]. Nevertheless, in many dogs, both tachyand bradyarrhythmia might be paroxysmal, and event monitors were rarely used in our study. Thus, an association between the presence of arrhythmias and syncopal episodes cannot be definitively ruled out.

In this study, arrhythmias were reported in 9% of the dogs suggesting that rhythm disorders are rel- atively uncommon in our population. This is in agreement with the result of a previous study that showed a prevalence of arrhythmias, detected with an ECG, in 4% of dogs with MMVD [20]. How- ever, in other studies that used 24-h Holter monitoring, the prevalence of arrhythmias in dogs with MMVD was reported up to 90%, although these arrhythmias were clinically insignificant (e.g. occasional APCs) [32e34]. Therefore, the low number of dogs that presented with arrhythmias in our population might be secondary to a lower diagnostic accuracy of the ECG when compared to 24-h Holter monitoring in detecting arrhythmias represented by isolated events, rather than a true low incidence. Our results showed that supra- ventricular arrhythmias, particularly AF and APCs, were correlated with the severity of disease and the degree of LA enlargement. These findings are in agreement with the results of a previous study, where 24-h Holter monitoring was used to assess the prevalence of arrhythmias in dogs with MMVD [33]. Left atrial stretch has been suggested as a possible cause of the development of supra- ventricular arrhythmias in dogs with MMVD [35,36].

In our study, the HR detected during the phys- ical examination was associated with the severity of the disease. The prevalence of sinus arrhythmia, identified by ECG, was lower in dogs with CHF and in dogs with chamber enlargement than in dogs that did not share those characteristics. Sinus arrhythmia is a common finding in healthy dogs and is determined by momentary changes in para- sympathetic and sympathetic balance. Increased activity of the sympathetic nervous system along with a decrease parasympathetic activity has been reported in dogs with experimental MR [37,38]. While the altered activity of the autonomic nervous system in dogs with MMVD has been demon- strated using 24-h Holter monitoring, to the author's knowledge, this is the first time that both physical examination and ECG findings suggest an increase in sympathetic tone and a decrease in parasympathetic activity not only in dogs with CHF but also in dogs with chamber enlargement [34]. Interestingly, 9% of dogs in Stage-C had sinus arrhythmia. This might be explained by the fact that both dogs with acute and chronic CHF were included in our Stage-C. While the presence of respiratory sinus arrhythmia is virtually impossible in patients with acute CHF, in some dogs properly treated for CHF, respiratory sinus arrhythmia might be present.

Our results showed that the majority, but not all dogs with soft murmurs, are in Stage-B1, suggest- ing that soft murmurs are usually indicative of an early stage of MMVD. Several studies have found a relationship between the severity of disease and the intensity of the murmur in dogs with MMVD. However, all these studies were conducted in small breed dogs (<20 kg) [39,40]. When large breed dogs were included, no association was found between the intensity of the murmur and the severity of the disease [20]. Our results showed an association, independent of body size, between the intensity of the murmur and both the stage of the disease and the degree of LA enlargement determined by LA:Ao. An earlier study that included a similar proportion of large and small breed dogs failed to find this association. This discrep- ancy may be explained by the fact that in that study, murmurs were classified as low/moderate and high intensity and that a description of the murmur was lacking in 20% of the population [20].

While the presence of a left apical systolic murmur is the most common reason for referral in dogs affected by MMVD, not all dogs in our study had a heart murmur. Some dogs in our study

were referred for further evaluation of syncopal epi- sodes, rhythm disturbances, the presence of cough, or the perception of radiographic cardiomegaly.

MMVD is characterized by volume overload and the development of LA enlargement and left ven- tricular eccentric hypertrophy as the disease progresses. The VHS is commonly used in veterinary medicine to assess the presence of radiographic cardiomegaly [14]. Our results showed a positive correlation between VHS and LA:Ao as well as between VHS and LVIDd_N, the latter being an echocardiographic measure that is commonly used to assess the degree of left ventricular dilation. However, our findings also showed that car- diomegaly was identified by VHS in 33% of the dogs with normal echocardiographic LA and left ven- tricle chamber dimensions. Moreover, the VHS failed to identify cardiomegaly in 14e21% of dogs with echocardiographic LA and left ventricular enlargement. Although the side of recumbency, respiratory phase, and breed variability have been reported, our findings suggest that VHS might fail to identify the presence/absence of cardiomegaly, and additional data are needed to further evaluate specificity and sensitivity of the VHS in the detection of heart enlargement [17,41e43].

Our results suggest that systolic myocardial dysfunction, defined by an LVIDs_N greater than 1.26, is an uncommon finding in dogs with MMVD, accounting for 5% of the dogs in our population. As previously reported, we showed that the preva- lence of systolic dysfunction was greater in dogs with a BW ! 20 kg [5]. However, 240 dogs with an LVIDs_N above the reference range had a BW < 20 kg. This result suggests that, even if uncommon, some small breed dogs also have sys- tolic dysfunction, at least based on LVIDs_N. The evaluation of systolic function in patients with volume overload is challenging because all echo- cardiographic indices commonly used to estimate systolic function are load dependent [44]. In vet- erinary medicine, the LVIDs_N, even if load dependent, is commonly used to evaluate systolic function. While depressed contractility in human patients with MR is well characterized, the role of systolic dysfunction in dogs with MMVD is still controversial, particularly in small breed dogs [45,46]. Although LVIDs_N is not independent of cardiac loading conditions, it is subject to fewer influences than the ejection phase indices such as fractional shortening. Our results suggest that a small subset of patients with MMVD, regardless of body size, develop systolic dysfunction as the dis- ease progresses.

We reported a prevalence of concomitant disease in approximately 40% of our population. Dogs affected by MMVD are usually middle-aged to older dogs and, therefore, are more likely to develop other chronic conditions [47]. Our results show that the prevalence of con- comitant diseases is higher in dogs in Stage-B1 and dogs in Stage-B2 when compared with dogs in Stage-C. Identification of a murmur in dogs with clinical signs caused by a non-cardiac disease might represent a common reason for referral and partially explain this finding. Chronic respiratory diseases were by far the most common comorbidity in our population, and no association was found between their prevalence and the stage of MMVD. Because we studied a relatively unselected population and because of the large number of dogs enrolled, our results are clinically relevant and general- izable to the real-world practice setting.

Limitations

This study has limitations. First, our population consisted of dogs examined at specialty referral centers. Therefore, our findings might reflect a referral bias and not represent the general pop- ulation. However, most of the dogs in our study did not have clinical signs of CHF or echocardiographic evidence of LA and left ventricular enlargement. Moreover, based on the large number of patients enrolled, the large proportion of mixed breed dogs, and because the only inclusion criterion was the presence of MMVD, it is reasonable to assume that results of

our study may be extrapolated to the larger population of dogs affected by MMVD. Second, a tendency toward missing data is an inherent limitation of disease registries. However, this limitation is partly overcome by large sample sizes compared to clinical trials. Third, data were collected by several different operators, and interoperator variability was not assessed. Nevertheless, standardized methods were used to obtain both echocardiographic and thoracic radiographic measurements; therefore, this should not have had a relevant impact on our results.

It should be pointed out that while data have been checked for data entry errors, measurement errors may be present since a review of each measurement on the single echocardiogram was not performed. Although we consider this type of error uncommon, since most of the reports are reviewed before being finalized, this represents an intrinsic limitation of disease registries, and interpretation of extreme values should be carefully made.

In some dogs, the TR velocity reported was very low. This finding could be partly explained by technical issues such as inadequate align- ment of blood flow with the ultrasound beam or image quality. However, it is uncommon that dogs with clinically significant PH have trace or mild TR that would lead to improper alignment with the jet; therefore, our results on patients diagnosed with PH should be valid.

Dogs in Stage-C were classified based on the presence of clinical signs of CHF that responded to medical treatment and/or on the presence of radiographic evidence of CHF. Even if the presence of clinical signs is a reliable method commonly used in clinical practice, thoracic radiographs remain the criterion standard for the assessment of CHF in dogs. Therefore, misdiagnoses of some dogs cannot be excluded.

Lastly, the execution of additional diagnostic tests, as well as, in some cases, the presumptive diagnosis of concomitant diseases, was based on

the clinical judgment of the cardiologist after careful consideration of the patient history, clinical signs, and diagnostic findings. Therefore, misdiagnoses of concomitant diseases in some dogs cannot be ruled out.

Conclusions

This study confirms that a disease registry repre- sents a valuable tool that can be used in veteri- nary medicine to prospectively collect data on a specific disease. Results of this large study on a relatively unselected population of dogs affected by MMVD mainly confirm what has been previously reported. However, we provide new findings like the presence of systolic dysfunction in some small breed dogs and the association between the intensity of murmur and the severity of the dis- ease regardless of the body size, which may have clinical relevance in the assessment of dogs affected by this disease.

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Tables and Figures

Table 1 Distribution of the 20 most common breeds.

	Total classified n = 6016	Stage-B1 n = 3891	Stage-B2 n = 889	Stage-C n = 1236
Mixed Breed	n = 1563 26%	n = 1025 26%	n = 249 28%	n = 289 23%
CKCS	n = 491 8%	n = 340 9%	n = 74 8%	n = 77 6%
Chihuahua	n = 483 8%	n = 264 7%	n = 80 9%	n = 139 11%
Shih-Tzu	n = 298 5%	n = 195 5%	n = 33 4%	n = 70 6%
Maltese	n = 218 4%	n = 103 3%	n = 45 5%	n = 70 6%
Beagle	n = 205 3%	n = 139 4%	n = 26 3%	n = 40 3%
Dachshund	n = 201 3%	n = 138 4%	n = 28 3%	n = 35 3%
Pomeranian	n = 189 3%	n = 103 3%	n = 38 4%	n = 48 4%
Yorkshire Terrier	n = 172 3%	n = 108 3%	n = 23 3%	n = 41 3%
Cocker Spaniel	n = 138 2%	n = 99 3%	n = 16 2%	n = 23 2%
Boston Terrier	n = 125 2%	n = 77 2%	n = 21 2%	n = 27 2%
Miniature Schnauzer	n = 116 2%	n = 68 2%	n = 21 2%	n = 27 2%
Poodle	n = 94 2%	n = 62 2%	n = 9 1%	n = 23 2%
Miniature Poodle	n = 91 2%	n = 54 1%	n = 12 1%	n = 25 2%
JRT	n = 82 1%	n = 54 1%	n = 13 2%	n = 15 1%
Bichon Frisè	n = 73 1%	n = 45 1%	n = 11 1%	n = 17 1%
Havanese	n = 63 1%	n = 34 1%	n = 13 2%	n = 16 1%
Labrador Retriever	n = 56 0.9%	n = 42 1%	n = 4 0.5%	n = 10 0.8%
Toy Poodle	n = 54 0.9%	n = 34 0.9%	n = 10 1%	n = 10 0.8%
Schnauzer	n = 48 0.8%	n = 31 0.8%	n = 12 1%	n = 5 0.4%

Table 2a Signalment of the 6016 dogs enrolled and classified by stage.

	Total classified n = 6016	Stage-B1 n = 3891	Stage-B2 n = 889	Stage-C n = 1236
Age	10 (1–19)	10 (1–19)[a]	11 (1–17)[b]	11 (1–18)[c]
	n = 6016	n = 3891	n = 889	n = 1236
Body Weight	7.9 (1–82.4)	8.4 (1–71.8)[a]	7.1 (1.7–47.2)[b]	7.0 (1–82.4)[b]
	n = 6012	n = 3891	n = 889	n = 1232
<20 kg	n = 5275	n = 3.316[a]	n = 836[b]	n = 1,123[c]
	88%	85%	94%	91%
Sex				
Male	n = 3163	n = 2,030[a]	n = 491[a]	n = 642[a]
	53%	52%	55%	52%
Female	n = 2853	n = 1,861[a]	n = 398[a]	n = 594[a]
	47%	48%	45%	48%

Within the same row, values with the same letter in the superscript did not differ significantly, while different letters in the superscript indicate a significant difference ($p<0.05$).

Table 2b History of the 6016 dogs enrolled and classified by stage.

	Total classified n = 6016	Stage-B1 n = 3891	Stage-B2 n = 889	Stage-C n = 1236
RRH	n = 891	n = 371	n = 94	n = 426
	15%	10%	11%	34%
Normal	n = 422	n = 268[a]	n = 80[a]	n = 74[b]
	7%	7%	9%	6%
Dyspnea	n = 200	n = 32[a]	n = 3[a]	n = 165[b]
	3%	1%	0.3%	13%
Tachypnea	n = 228	n = 43[a]	n = 7[a]	n = 178[b]
	4%	1%	1%	14%
Panting	41	n = 28	n = 4	n = 9
	1%	1%	0.5%	1%
Cough	n = 2375	n = 1,123[a]	n = 393[b]	n = 859[c]
	39%	29%	44%	70%
Syncope	n = 369	n = 125[a]	n = 50[b]	n = 194[c]
	6%	3%	5%	16%

RRH: respiratory rate at home. Within the same row, values with the same letter in the superscript did not differ significantly, while different letters in the superscript indicate a significant difference ($p<0.05$).

Table 2c Physical examination findings of the 6016 dogs enrolled and classified by stage.

	Total classified n = 6016	Stage-B1 n = 3891	Stage-B2 n = 889	Stage-C n = 1236
RRPE	n = 4444	n = 2.810	n = 630	n = 1.004
	74%	72%	71%	82%
Normal	n = 2634	n = 1,975[a]	n = 368[a]	n = 291[b]
	44%	51%	41%	24%
Dyspnea	n = 44	n = 5[a]	n = 2[a]	n = 37[b]
	1%	0.1%	0.2%	3%
Tachypnea	n = 696	n = 171[a]	n = 67[a]	n = 458[b]
	12%	4%	7.5%	37%
Panting	1070	n = 659	n = 193	n = 218
	18%	17%	22%	18%
Abdominal effusion	n = 71	n = 12[a]	n = 3[a]	n = 56[b]
	1%	0.3%	0.3%	5%
Murmur	n = 6006	n = 3887	n = 886	n = 1231
	99.8%	99.9%	99.7%	99.5%
Yes	n = 5785	n = 3,673[a]	n = 884[b]	n = 1,228[b]
	96%	94%	99.7%	99.5%
No	n = 220	n = 215[a]	n = 2[b]	n = 3[b]
	4%	6%	0.3%	0.2%
Intensity	n = 5777	n = 3.672	n = 885	n = 1.220
Soft	n = 1171	n = 1,134[a]	n = 16[b]	n = 21[b]
	20%	31%	2%	2%
Moderate	n = 1671	n = 1,391[a]	n = 175[b]	n = 105[c]
	29%	38%	20%	9%
Loud	n = 1960	n = 983[a]	n = 460[b]	n = 517[c]
	34%	27%	52%	42%
Palpable	n = 974	n = 165[a]	n = 232[b]	n = 577[c]
	17%	5%	26%	47%[a]
HR bpm	120 (30–280) n = 5882	120 (30–250)[a] n = 3805	130 (38–200)[b] n = 868	144 (36–280)[c] n = 1209
SBP	138 (45–280) n = 4826	140 (58–280)[a] n = 3094	138 (63–230)[a] n = 740	128 (45–230)[b] n = 992

HR: heart rate during the physical examination; RRPE: respiratory rate during the physical examination; SBP: systolic blood pressure. Within the same row, values with the same letter in the superscript did not differ significantly, while different letters in the superscript indicate a significant difference ($p<0.05$).

Table 3 Electrocardiographic findings of the 6016 dogs enrolled and classified by stage.

	Total classified n = 6016	Stage-B1 n = 3891	Stage-B2 n = 889	Stage-C n = 1236
Sinus Arrhythmia	1359	1,092[a]	168[b]	99[c]
	23%	28%	19%	8%
APCs	212	92[a]	30[b]	90[c]
	4%	2%	3%	7%
VPCs	197	107[a]	35[a,b]	55[b]
	3%	3%	4%	5%
II and III AVB	63	51[a]	7[a]	5[b]
	1%	1%	1%	0.4%
AF	61	5[a]	3[b]	53[c]
	1%	0.1%	0.4%	4%
SVT	39	16[a]	2[a]	21[b]
	0.6%	0.4%	0.2%	2%
VT	20	12[a]	2[a]	6[a]
	0.3%	0.3%	0.2%	0.5%
SSS	2	2[a]	0[a]	0[a]
	0.03	0.1%	/	/

AF: atrial fibrillation; APC: atrial premature complex; AVB: atrioventricular block; SSS: sick sinus syndrome; SVT: supraventricular tachycardia; VPC: ventricular premature complex; VT: ventricular tachycardia. Within the same row, values with the same letter in the subscript did not differ significantly, while different letters in the superscript indicate a significant difference ($p<0.05$).

Table 4 Thoracic radiographs of the 6016 dogs enrolled and classified by stage.

	Total classified n = 6016	Stage-B1 n = 3891	Stage-B2 n = 889	Stage-C n = 1236
	N	N	N	N
Thoracic Radiograph	1667 28%	716 19%	226 25%	725 59%
VHS	11.2 (8—13.5) n = 1358	10.5^{a} (8—13.5) n = 626	11.4^{b} (8.9—13.5) n = 203	12^{c} (8.8—14.5) n = 529
Pulmonary edema	530	0^{a}	0^{a}	530^{b}
Airways Collapse	334	121^{a}	73^{a}	140^{b}

VHS: vertebral heart score. Within the same row, values with the same letter in the subscript did not differ significantly, while different letters in the superscript indicate a significant difference ($p<0.05$).

Table 5 Baseline echocardiographic findings of the 6016 dogs enrolled and classified by stage.

	Total n = 6016	Stage-B1 n = 3891	Stage-B2 n = 889	Stage-C n = 1236
LA:Ao	1.44 (0.58—4.24) n = 6006	1.31^{a} (0.58—2.37) n = 3891	1.82^{b} (1.6—3.18) n = 889	2.11^{c} (1.08—4.24) n = 1226
LVIDd_N	1.69 (0.74—3.36) n = 5997	1.58^{a} (0.73—3.19) n = 3891	1.95^{b} (1.70—3.10) n = 889	2.09^{c} (1.04—3.36) n = 1217
LVIDs_N	0.89 (0.26—2.19) n = 5986	0.85^{a} (0.26—1.9) n = 3883	0.99^{b} (0.52—1.72) n = 888	1.01^{b} (0.31—2.19) n = 1215
TR peak velocity m/s	2.78 (0.27—6.37) n = 4337	2.63^{a} (0.27—6.37) n = 2589	2.83^{b} (0.67—5.61) n = 692	3.26^{c} (0.70—5.83) n = 1056
PH yes	n = 1567 26%	n = 588^{a} 15%	n = 265^{b} 30%	n = 714^{c} 58%
ePAP > 55 mmHg	n = 385 6%	n = 57 1%	n = 49 6%	n = 279 23%
E peak m/s	0.90 (0.26—3.02) n = 5795	0.78^{a} (0.26—2.85) n = 3756	1.13^{b} (0.48—2.68) n = 869	1.38^{c} (0.35—3.02) n = 1170

E max: E wave maximum velocity; ePAP: estimated pulmonary arterial pressure; LA:Ao: left atrium—aortic ratio; LVIDd_N: left ventricle internal diameter at end-diastole indexed by body size; LVIDs_N: left ventricle internal diameter at end-systole indexed by body size; PH: pulmonary hypertension; TR: tricuspid regurgitation. Within the same row, values with the same letter in the subscript did not differ significantly, while different letters in the superscript indicate a significant difference ($p<0.05$).

Table 6 Comorbidities of the 6016 dogs enrolled and classified by stages.

	Total n = 6016	Stage-B1 n = 3891	Stage-B2 n = 889	Stage-C n = 1236
Comorbidities	n = 2459 41%	n = 1682 (43%)	n = 359 (40%)	n = 418 (34%)
Chronic respiratory diseases	n = 843 14%	n = 539 14%	n = 135 15%	n = 169 14%
Azotemia	n = 380 6%	n = 250 6%	n = 48 5%	n = 82 7%
Orthopedic diseases	n = 330 5%	n = 237 6%	n = 44 5%	n = 49 4%
Neoplasia	n = 267 4%	n = 205 5%	n = 30 3%	n = 32 3%
Neurologic diseases/ signs	n = 267 4%	n = 180 5%	n = 52 6%	n = 35 3%
Systemic hypertension	n = 244 4%	n = 169 4%	n = 37 4%	n = 38 3%
Gastrointestinal and hepatobiliary disease and/or symptoms	n = 204 3%	n = 139 4%	n = 34 4%	n = 31 3%
Hypothyroidism	n = 158 3%	n = 98 3%	n = 27 3%	n = 33 3%
Genitourinary diseases	n = 141 2%	n = 101 3%	n = 19 2%	n = 21 2%
Hyperadrenocorticism	n = 105 2%	n = 75 2%	n = 9 1%	n = 21 2%
Dermatologic diseases	n = 84 1%	n = 67 2%	n = 10 1%	n = 7 0.6%
Diabetes mellitus	n = 64 1%	n = 55 1%	n = 8 0.9%	n = 1 0.1%
Other endocrine diseases	n = 26 0.4%	n = 22 0.6%	n = 1 0.1%	n = 3 0.2%
Immune-mediated diseases	n = 17 0.3%	n = 13 0.3%	n = 1 0.1%	n = 3 0.2%

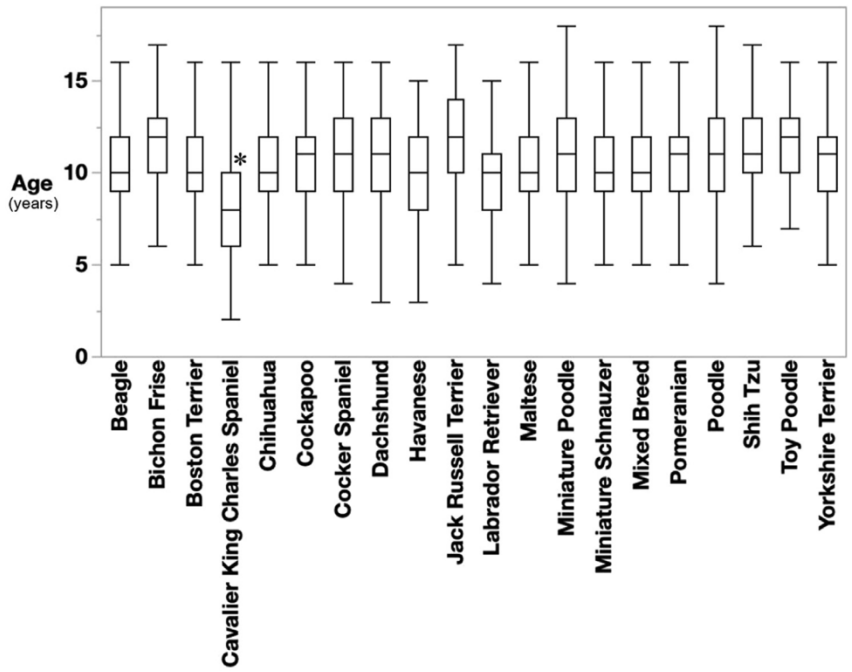

Fig. 1 Box and whisker plot of age at enrollment of the 20 most common breeds. Cavalier King Charles Spaniels were younger (*) when compared with other breeds.

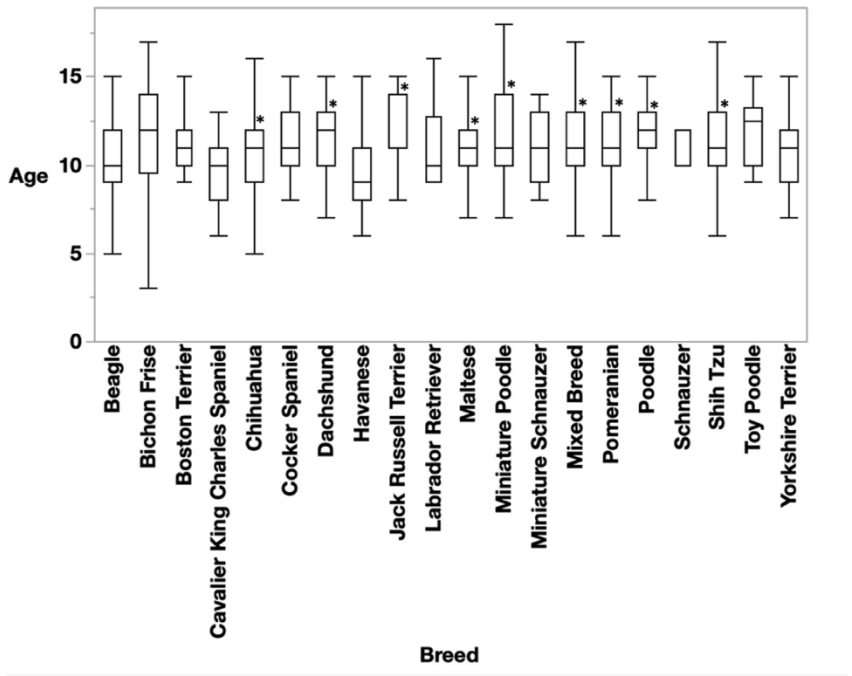

Fig. 2 Box and whisker plot of age at enrollment of the 20 most commonly affected breeds presenting in ACVIM Stage-C. Cavalier King Charles Spaniels were younger when compared with some of the other breeds (*).

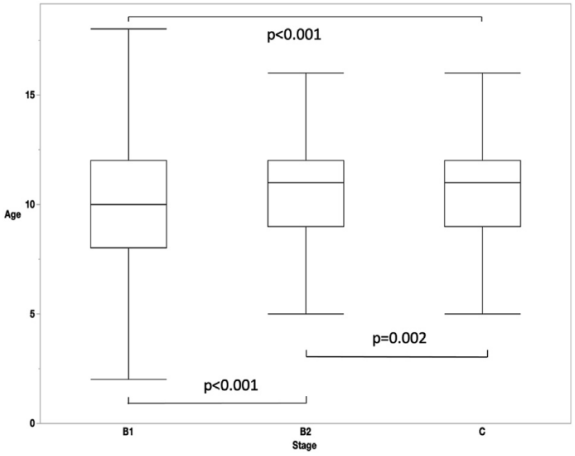

Fig. 3 Association between the age at enrollment and the ACVIM stage of the disease. Dogs in Stage-B1 were younger, and dogs in Stage-C were older when compared with dogs in other stages.

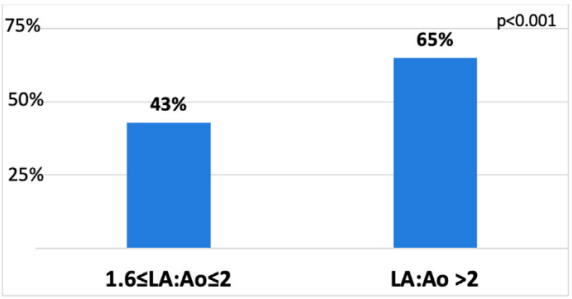

Fig. 4 Prevalence of cough in dogs without radiographic evidence of pulmonary edema or concomitant respiratory diseases based on left atrial size. Dogs with a severe left atrial enlargement (left atrium to aortic root ratio (LA:Ao) $>$ 2) were more likely to present with cough than dogs with mild to moderate left atrial enlargement ($1.6 \leq$ LA:Ao ≤ 2) ($p<0.001$).

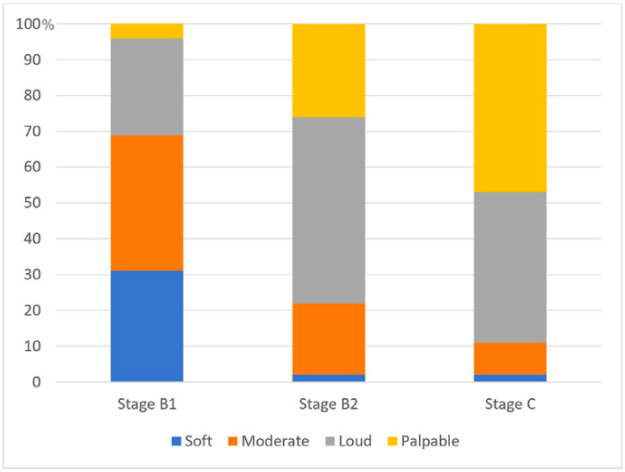

Fig. 5 Association between murmur intensity and the ACVIM Stage. Increasing murmur intensity is associated with the increased severity of the disease.

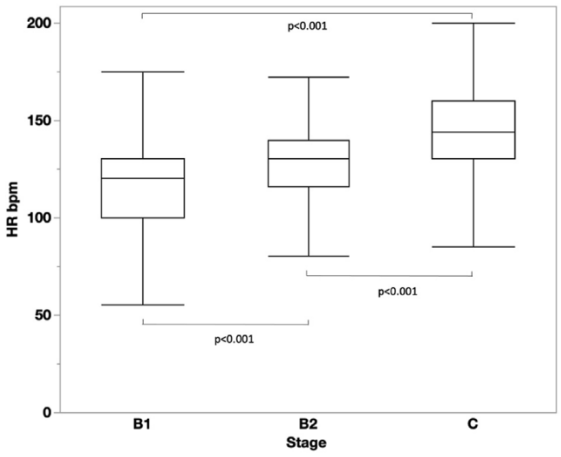

Fig. 6 Association between the heart rate detected during the physical examination and severity of the disease. Bpm: beats per minute; HR: heart rate.

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