DEGENERATIVE MITRAL VALVE DISEASE: SURVIVAL OF DOGS ATTENDING PRIMARY-CARE PRACTICE IN ENGLAND

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SUMMARY

This study aimed to evaluate survival of dogs with degenerative mitral valve disease (DMVD). A retrospective cohort study of dogs with DMVD attending primary-care practices in England was undertaken. Cases of DMVD were identified within the electronic patient records (EPRs) of practices sharing data with VetCompass. Kaplan-Meier curves were used to explore survival and Cox regression models identified factors associated with hazard of death.

The EPRs from 111,967 dogs, attending 93 veterinary practices between January 2010 and December 2011 identified 405 cases diagnosed with DMVD giving a prevalence of diagnosed DMVD of 0.36% (95% CI: 0.29 – 0.45%). A further 3,557 dogs were classified as possible cases (heart murmurs consistent with DMVD). Overall, a total of 3,962 dogs were classified as heart murmur cases (possible and diagnosed DMVD), giving a prevalence of 3.54% (95% CI: 3.26 – 3.84%).

One hundred and sixteen (28.6%) of the diagnosed DMVD cases were incident, newly diagnosed with DMVD. The mean age at diagnosis was 9.52 years (95% CI: 8.98 – 10.14 years). Fifty-eight (50.0%) of the incident cases died during the study period. The median survival time (MST) for all-cause mortality was 25.4 months (95% CI: 20.4 – 34.4 months) after disease detection for DMVD cases. For possible cases, 121 (29.7%) from a random sample of 407 possible DMVD cases were incident cases (newly detected heart murmur consistent with DMVD during the study period). The mean age at which a heart murmur was first recorded in possible cases was 9.73 years (95% CI: 9.02 – 10.44 years). Forty-nine (40.5%) possible cases died during the study period. The MST for all-cause mortality was 33.8 months (95% CI: 23.7 – 43.1 months) after a heart murmur was initially detected. In the multivariable survival analysis for possible and diagnosed cases, Cavalier King Charles Spaniels (CKCSs) and other purebreds had higher hazards of death than crossbreds. Dogs

weighing ≥ 20.0 kg and older dogs had an increased hazard of death compared with those < 20.0 kg and younger dogs, respectively.

The study highlights poorer survival for all-cause mortality in CKCSs and larger dogs. The reported survival characteristics could aid veterinary surgeons' advice on the prognosis for dogs with DMVD and help the assessment of the impact of the condition at a population level.

KEY WORDS epidemiology, primary-care practice, cardiac, survival, canine

INTRODUCTION

Degenerative mitral valve disease (DMVD) has a high prevalence in the domestic dog population, with estimates ranging between 3.5% - 69.7% (Detweiler & Patterson, 1965; Whitney, 1974; Thrusfield et al., 1985). The disorder is generally straightforward to diagnose from the presence of a characteristic heart murmur (Borgarelli & Haggstrom, 2010). However, dogs with DMVD form a heterogeneous population and only a proportion of affected animals will develop congestive heart failure or die as a result of their cardiac disease (Borgarelli et al., 2012). Hence a major challenge for practitioners centres on prognostication and identifying patients at greater risk of death.

Survival times have been reported for cohorts of dogs with DMVD recruited to clinical trials (Ettinger et al., 1998; The Bench Study Group, 1999; Haggstrom et al., 2008) and those included in observational studies monitored by specialist veterinary cardiologists (Borgarelli et al., 2008; Moonarmart et al., 2010; Borgarelli et al., 2012; Hezzell et al., 2012). Data from specialist-treated populations may be poorly generalizable to wider DMVD populations because referral caseloads may include complex cases requiring more advanced care (Bartlett et al., 2010) and non-consent bias may occur if patients enrolled into clinical trials are not representative of more general populations (Marcus, 1997). Further, the time of entry into

existing survival studies was generally defined as the time of referral or randomization, rather than the time the disease was initially detected, limiting the application of these results to the primary-care setting. The current literature on primary-care practice populations of dogs with DMVD lacks median survival time (MST) estimates from the time of disease detection to time of death.

Risk stratification could improve prognosis and management of DMVD cases. For example, more frequent monitoring or targeted therapy may be warranted in patients at high risk of progressive disease (Hezzell et al., 2012). Previous survival studies have largely focussed on the predictive value of echocardiographic and radiographic measurements (Haggstrom et al., 2008; Moonarmart et al., 2010; Lord et al., 2011; Borgarelli et al., 2012; Hezzell et al., 2012; Reynolds et al., 2012) and circulating concentrations of cardiac biomarkers (Fonfara et al., 2010; Moonarmart et al., 2010; Hezzell et al., 2012; Eriksson et al., 2014) in dogs with DMVD. However, in primary-care practice, these diagnostic tests are often omitted due to limited availability of equipment, lack of clinical expertise or financial constraints. Some of these studies also evaluated the prognostic value of demographic variables, such as sex, breed, age and bodyweight (Haggstrom et al., 2008; Moonarmart et al., 2010; Hezzell et al., 2012; Reynolds et al., 2012), which can be easily derived from primary-care data. However, the latter studies yielded conflicting results and may have limited external validity as their study populations were managed by specialist veterinary cardiologists, which may be subject to selection bias.

Estimating MST and evaluating the predictive value of demographic factors in the primary-care setting would be of value as these results would be relevant to the wider primary-care population and could aid prognostication. The objectives of this study were to estimate the MST of dogs with DMVD and to identify demographic risk factors associated with all-cause

mortality in affected animals attending primary-care veterinary practices in England. It was hypothesised that crossbred dogs would have a lower hazard of death than purebred dogs.

MATERIALS AND METHODS

A retrospective cohort study followed cases of DMVD identified within the electronic patient records (EPRs) of dogs attending veterinary practices sharing de-identified data with the Veterinary Companion Animal Surveillance System database (VetCompass, 2014) between 1st January 2010 and 31st December 2011. The practices were primary-care companion animal practices, both independent and corporate, that had been recruited via publication of letters requesting participation of interested practices in the veterinary press and journals, regional meeting and presentations, and in response to enquiries from practices themselves. They were mainly located in central and southeast England. Data shared included demographic (date of birth, sex, breed, bodyweight, insurance status, microchip number, partial postcode, veterinary practice ID) and clinical data (free-text clinical notes, VeNom diagnostic terms (VeNom Coding Group, 2014), and treatments prescribed). The study received ethics approval from the Royal Veterinary College ethics and welfare committee.

Case finding was achieved by searching for EPRs containing key diagnostic terms relating to DMVD (e.g. 'mitral', 'valv*', 'MVD', 'murm*') and reviewing the free text clinical notes of potential cases. Two case definitions were developed to account for different levels of diagnosis: diagnosed DMVD and possible DMVD cases. Diagnosed DMVD cases were defined as dogs with a stated diagnosis of DMVD (or synonym) in their clinical notes or VeNom diagnostic terms. Possible DMVD cases were defined as dogs over one year old with a documented heart murmur consistent with DMVD without a specific cardiac diagnosis. Dogs reported to have continuous or diastolic murmurs were excluded as cases. Dogs with murmurs that had only been detected during pregnancy or that presented with other clinically significant

systemic disease (e.g. moderate to severe anaemia, pyrexia, severe hypovolaemia or dehydration) were also excluded. Dogs reported to have murmurs or mitral valve regurgitation due to other diagnosed cardiac disorders (e.g. aortic stenosis, ventricular septal defects etc.) were additionally excluded. Where a murmur was recorded and no evidence of any of the above criteria for exclusion was documented, the dog was classified as a possible DMVD case. Evidence of a point of maximal intensity (thoracic location where the heart murmur is heard most loudly) inconsistent with DMVD on chest auscultation was not used as an exclusion criterion. Diagnosed and possible DMVD cases were combined to form a population of dogs with heart murmurs consistent with DMVD for the prevalence estimates, hereafter described as heart murmur cases. Incidence estimates were reported separately for possible and diagnosed cases.

The EPRs of all diagnosed cases up to May 2014 were examined in detail. The date of the first veterinary consultation, the date the disease was detected and the date, cause and modality of death were extracted, where applicable. Incident cases were defined as dogs that were newly diagnosed with DMVD or recorded with a heart murmur during the study period. Dogs alive at the end of the study period were censored on the date of the last entry in their clinical notes. Death as a result of cardiac disease (cardiac death) was defined as euthanasia or death due to worsening of clinical signs associated with DMVD or when veterinary surgeons stated that heart disease was the primary cause of death in the clinical notes. Cases were not classified as cardiac deaths if alternative or multiple causes of death were listed, or if the cause of death was not specified. Due to the large number of possible cases and the time required to review each case's clinical records, a random sample of possible DMVD cases was selected from the denominator of all possible cases using an electronic random number generator (www.random.org) to enable comparison between the survival of diagnosed and possible cases. The number of possible cases randomly selected was based on providing a similar number of

cases as evaluated for the diagnosed cases in order to provide a similar level of statistical power to detect major risk factors. The date of murmur detection and the date, cause and modality of death in incident possible cases were recorded.

Data were exported to a spreadsheet (Microsoft Office Excel 2010, Microsoft Corp, Redmond, WA), checked, cleaned and exported to Stata Version 13 (Stata Corporation, TX) for analysis. Prevalence and 95% confidence intervals (95% CI) were calculated for heart murmur cases (including both diagnosed and possible cases) and for diagnosed DMVD cases only. Prevalence was adjusted for clustering at the practice level using survey commands (StataCorp., 2013). Further analyses relate to incident cases only.

The MST for all-cause mortality and cardiac death were calculated for diagnosed and possible cases, when possible. Kaplan-Meier survival curves were generated for all-cause mortality and cardiac-related death and log-rank tests were used to explore survival differences between diagnosed and possible cases. Univariable and multivariable Cox proportional hazard models were used to evaluate associations between the following explanatory variables and hazard of death (all-cause mortality): breed, sex, insurance status, maximum recorded bodyweight (kg), age at diagnosis (years) and level of diagnosis (diagnosed and possible cases). Breeds were categorised into 'crossbred', 'Cavalier King Charles Spaniel' (CKCS) and 'other purebred'. CKCS were evaluated as a separate group as this represented the most common breed within the data and has frequently been a comparator group in the current literature (Haggstrom et al., 2008). Additional analyses evaluating a binary breed variable ('purebreds' and 'crossbreds') were performed. Maximum bodyweight was further dichotomised based on published literature (< 20.0 kg and ≥ 20.0 kg) (Borgarelli et al., 2004; Borgarelli et al., 2012). Age at diagnosis (years) was categorised into four groups (< 5.0, 5.0 - < 10.0, 10.0 - < 15.0, and ≥ 15.0 years) and evaluated for a linear trend association. Level of diagnosis and breed

were forced variables in the model to account for the sampling technique and *a priori* interest, respectively. Variables significant at the 20% level in univariable analyses were taken forward for consideration in the mixed effects multivariable model. Manual stepwise backward elimination regression was used to sequentially remove variables with a P-value > 0.05 in the multivariable model (Dohoo et al., 2009). Each eliminated variable was then added to the final model to assess for important confounding by the change in parameter estimates. First order interactions between final model explanatory variables were evaluated. Veterinary practice was evaluated as a shared frailty term to account for clustering at the practice-level. The proportional hazards assumption was tested using Schoenfeld residuals and visual inspection of log-cumulative hazard and Kaplan-Meier Cox plots. Goodness of fit was evaluated using Cox-Snell residuals. Dogs with any missing data for the risk factors of interest were excluded from the multivariable Cox proportional hazards model.

It was estimated that a sample size of approximately 160 individuals would be required to detect a hazard ratio (HR) for all-cause mortality of two for a variable to which 75% of individuals were exposed, at a confidence level of 95% and power of 80%. This calculation was based on the estimated proportion of purebred dogs in the VetCompass database (O'Neill et al., 2014), an accrual time of 24 months, a follow-up time of 24 months and a MST of 20 months for exposed individuals (PS Power and Sample Size Calculations, 2014).

RESULTS

Descriptive statistics

The denominator population consisted of 111,967 individual dogs attending 93 veterinary practices on one or more occasions between 1st January 2010 and 31st December 2011. Four hundred and five dogs were identified as having a diagnosis of DMVD, giving a prevalence,

177 adjusted for the clustering effect of practice, of 0.36% (95% CI: 0.29 – 0.45%). A further 3,557
178 dogs were classified as possible cases, having a heart murmur consistent with DMVD recorded
179 within their EPRs. Generally, the age, bodyweight and breed distributions of possible and
180 diagnosed DMVD cases were similar; with DMVD typically affecting older small- to medium-
181 sized dogs (data not shown). A total of 3,962 dogs were heart murmur cases (with possible or
182 diagnosed DMVD), giving a prevalence, adjusted for the clustering effect of practice, of 3.54%
183 (95% CI: 3.26 – 3.84%).

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185 Survival times of incident diagnosed and possible DMVD cases

186 Incident diagnosed DMVD cases: One hundred and sixteen (28.6%) of the 405 diagnosed
187 DMVD cases were incident cases, newly diagnosed with DMVD or recorded with a heart
188 murmur during the study period. The mean age at which DMVD was diagnosed or the presence
189 of a heart murmur was first recorded in diagnosed cases was 9.52 years (95% CI: 8.98 – 10.14
190 years). The median follow-up time was 17.9 months (IQR: 6.0 – 27.9 months, range: 0.0 – 45.2
191 months). Fifty-eight (50.0%) of the 116 incident diagnosed cases died during the study period.
192 Twenty of these 58 (34.5%) deaths were primarily due to cardiac disease, 9 (15.5%) deaths
193 occurred due to multiple causes including cardiac disease and 16 (27.6%) deaths occurred due
194 to non-cardiac causes. In 13 (22.4%) cases, cause of death was not recorded. Euthanasia
195 accounted for 43 (74.1%) of the 58 deaths. The MST for all-cause mortality was 25.4 months
196 (95% CI: 20.4 – 34.4 months) after the disease was initially detected (Table 1). MST for cardiac
197 death could not be calculated for these cases as the cumulative proportion of dogs surviving
198 failed to drop below 0.5.

199 Incident possible DMVD cases: One hundred and twenty one (29.7%) from a random
200 sample of 407 possible DMVD cases were incident cases, based on the presence of a heart

murmur consistent with newly detected DMVD during the study period. The mean age at which the presence of a heart murmur was first recorded in possible cases was 9.73 years (95% CI: 9.02 – 10.44 years). The median follow-up time for possible cases was 14.4 months (IQR: 2.5 – 27.6 months, range 0.0 – 43.5 months). Forty-nine (40.5%) possible cases died during the study period. Eight (16.3%) of the 49 deaths were primarily attributed to cardiac disease, two (4.1%) deaths occurred due to multiple causes including cardiac disease and 29 (59.2%) deaths occurred due to non-cardiac causes. In 10 (20.4%) of the 49 cases that died, cause of death was not recorded. Euthanasia accounted for 45 (91.2%) of the 49 deaths. The MST for all-cause mortality was 33.8 months (95% CI: 23.7 – 43.1 months) after a heart murmur was initially detected. MST for cardiac related death was 42.0 months (95% CI: 31.2 – 52.7 months). There was no evidence of a significant difference in the survival functions of diagnosed and possible DMVD cases for all-cause mortality (log rank test, P = 0.63) (Fig. 1). However, there was a statistically significant reduction in survival for cardiac mortality for diagnosed compared to possible cases (log rank test, P = 0.034) (Fig. 2).

Cox proportional hazards models: In the univariable analysis, there was a non-statistically significant trend for an association between breed and survival (P = 0.083). CKCS had a lower hazard of death than crossbred dogs (HR 0.44, 95% CI 0.21 – 0.96), whereas there was no difference observed between the survival of crossbreds and other purebreds. Dogs with a maximum recorded bodyweight of 20.0 kg or greater had almost twice the hazard of death in the univariable analysis (HR 1.87, 95% CI: 1.24 – 2.83). For each 5-year category increase in age, the hazard of death increased by a factor of 2.80 (95% CI: 2.09 – 3.75). There was no evidence of an association between survival and sex, insurance status or level of diagnosis (diagnosed versus possible cases) (Table 2). When CKCS were combined with other purebreds, no association between breed and survival was detected (P = 0.245). Twelve dogs had missing bodyweight data and 10 dogs did not have insurance status recorded.

In the multivariable analysis, CKCS (HR 2.78, 95% CI: 1.05 – 7.36) and other purebred dogs (HR 1.86, 95% CI: 1.07 – 3.23) had a higher hazard of death than crossbred dogs. Dogs weighing ≥ 20.0 kg had almost three times the hazard of death than dogs < 20.0 kg (HR 2.81, 95% CI: 1.72 – 4.59). For each 5-year age category increase, hazard of death increased 3.85 fold (95% CI: 2.61 – 5.69). Veterinary practice was included as a shared frailty term (P = 0.027). No major confounding (as represented by substantial variation in hazard ratios on addition of the second variable) or statistically significant interactions were identified. There was no evidence that the proportional hazards assumption was violated and the model diagnostics showed no evidence of lack of fit. When the breed variable with three groups (CKCS, other purebreds and crossbreds) was substituted for the binary breed variable (purebreds and crossbreds) in the multivariable model, the association between breed and survival persisted; with purebreds having approximately double the hazard of death compared with crossbred dogs (HR 1.84, 95% CI: 1.06 – 3.18).

DISCUSSION

This study identified a prevalence of diagnosed DMVD of 0.36% (95% CI: 0.29 – 0.45%) and a substantially greater proportion of dogs with heart murmurs consistent with DMVD (3.54%, 95% CI: 3.26 – 3.84%). The MST following detection of the disease was approximately 2 – 3 years in both diagnosed and possible DMVD cases. Purebreds, older dogs and those weighing ≥ 20.0 kg had a higher hazard of death compared with crossbreds, younger and lighter dogs, respectively.

The MSTs for all-cause mortality were 25.4 (95% CI: 20.4 – 34.4) and 33.8 (23.7 – 43.1) months for diagnosed and possible cases, respectively. Considering that the disease was initially detected in older dogs (mean age 9.52 and 9.73 years in diagnosed and possible cases, respectively) and the MST was relatively long, DMVD appeared to have minimal impact on longevity in many dogs. Further, the median age of death in our DMVD cohort was 12.2 years (IQR: 10.5 – 14.3 years), similar to median longevity reported for 5,095 dogs with confirmed deaths within the VetCompass population (12.0 years, IQR 8.9 – 14.2 years) (O'Neill et al., 2013). The median age of death of crossbreds (14.3 years, IQR: 12.3 – 15.2), purebreds (11.7 years, IQR: 10.0 – 13.6) and CKCS (10.0 years, IQR 8.6 – 10.7) in the current DMVD cohort were similar to those reported within the overall VetCompass population (13.1 years, IQR: 10.1 – 15.0; 11.9 years, IQR 8.4 – 14.0 and 9.9 years, IQR 8.1 – 12.3, respectively) (O'Neill et al., 2013). However, 34.5% of deaths among dogs with diagnosed DMVD were primarily due to their cardiac disease, emphasising that dogs with DMVD are a heterogeneous population and that it is therefore important to identify those most at risk of progressive disease and death. When only cardiac related deaths were considered, dogs with diagnosed DMVD had shorter survival times than possible cases. Given the age at detection of murmurs and disease in possible and diagnosed cases respectively were very similar and the shorter survival times of diagnosed DMVD cases, it would appear that dogs with more advanced cardiac disease may be more likely to receive a diagnosis and be classified as diagnosed DNVD and die sooner due to their more severe state of disease.

The estimated MST in the current study was generally longer than those reported in the literature. Two studies evaluating survival in dogs presenting to Italian referral centres reported MST of approximately 20 months for all-cause mortality (Borgarelli et al., 2008, Borgarelli et al., 2012). A cohort of dogs with DMVD enrolled to a research clinic in the UK had a MST of 11.1 months (range 0.1 – 32.7 months) (Moonarmart et al., 2010). Randomised controlled trials

evaluating different interventions in dogs with heart failure due to DMVD have reported MST from the time of randomisation until cardiac death or treatment failure. In the BENCH study, MST was 14.5 months in the intervention group and 5.0 months in the placebo group (The Bench Study Group, 1999). MST for dogs recruited to the LIVE and QUEST studies were approximately 5 - 6 months (Ettinger et al., 1998; Haggstrom et al., 2008). The discrepancies between the MST reported in the current study and those published in the literature may be due to differing inclusion criteria and primary end-points. The current study included dogs at all stages of the disease and the primary-end point was death, whereas some previous studies focused only on dogs with congestive heart failure and, for ethical reasons, included treatment failure among their primary end-points. A delay between disease detection by the primary-care practitioner and subsequent referral for inclusion into survival studies may also account for MST differences. Moreover, referral populations may be prone to preferentially select dogs with more advanced disease (Bartlett et al., 2010) than the entire canine DMVD population. The MSTs reported by the current study may thus be of greater relevance to primary-care practitioners, who manage most DMVD cases.

Cavalier King Charles Spaniels (HR 2.78, 95% CI: 1.05 – 7.36) and other purebred dogs (HR 1.86, 95% CI: 1.07 – 3.23) had a higher hazard of death than crossbred dogs in the multivariable analysis. Interestingly, in the univariable analysis, CKCS had a significantly decreased hazard of death (HR 0.44, 95% CI: 0.21 – 0.96) and purebreds had a similar hazard of death compared with crossbreds. The differences between the results of univariable and multivariable analyses were largely due to the confounding effect of age at diagnosis; CKCS and other purebreds were significantly younger when they developed DMVD compared with crossbred dogs and, after adjusting for age at diagnosis, the trend to reduced hazard in the purebred categories disappeared and these breeds were associated with increased hazard of death.

In the current study, dogs weighing 20 kg or more had nearly three times the hazard of death compared with dogs less than 20 kg (HR 2.81, 95% CI: 1.72 – 4.59). It has been suggested that heavier dogs and larger breed types with primary mitral valve disease may have a different clinical course compared with smaller dogs (Borgarelli et al., 2004). An alternative explanation for the association between survival and bodyweight in the current study population is that heavier dogs were more likely to be misclassified as DMVD cases. It is possible that some of these dogs had heart murmurs due to other causes, such as dilated cardiomyopathy, which is more common in large breeds and carries a poorer prognosis than DMVD (Martin et al., 2009). Finally, population-based studies consistently report that larger dogs have reduced longevity compared with smaller dogs (Michell, 1999; Galis et al., 2007; Greer et al., 2007; O'Neill et al., 2013). As the multivariable analysis in the current study explored only all-cause mortality, the association between bodyweight and hazard of death may reflect reduced longevity in general in larger dogs rather than cardiac deaths specifically.

In agreement with a previous study (Hezzell et al., 2012), there was strong evidence for an association between age and all-cause mortality in dogs with DMVD, with hazard of death increasing 3.85 fold (95% CI: 2.61 – 5.69) for each 5 year increase in age at diagnosis. In addition to being an independent predictor of outcome, age at diagnosis confounded the associations between breed and hazard of death, highlighting the importance of multivariable analyses when interpreting the effect of explanatory variables in epidemiological studies.

Including veterinary practice as a shared frailty term improved model fit, suggesting that practice-level factors influenced the outcome. The type of treatment administered has been reported to influence survival of dogs with DMVD (The Bench Study Group, 1999; Haggstrom et al., 2008), so if therapeutic management of cases within a practice are more similar than between practices, the survival experience of individuals attending the same practice may be

more similar than those of individuals from different practices. Further, most deaths resulted from euthanasia, rather than unassisted death. A poor prognosis given by the attending veterinary practitioner was identified as an important factor influencing the decision to euthanase dogs with congestive heart failure (Mallery et al., 1999). The timing of death may therefore be influenced by human factors and highlights the importance of optimising evidence-based prognostic guidelines.

This study had several limitations. Data were not originally recorded for research purposes but for clinical and billing reasons and were analysed retrospectively. Retrospective searching of the clinical records for key DMVD diagnostic terms may have missed some cases (false negatives) and incorrectly classified as positive others (false positives). In relation to specificity of search terms, this limitation was addressed by reviewing clinical records relating to a dog to minimise misclassification of non-DMVD dogs as cases. With regard to maximising sensitivity, the search strategy used was relatively broad (including use of truncated versions of key terms to allow for mis-spelling) and for DMVD a limited number of clinical terms are generally used by veterinary surgeons in practice, though inevitably some cases may have been missed. Further, if a practitioner did not perform thoracic auscultation or transcribe the DMVD diagnosis or the presence of a heart murmur into the EPR, an affected dog would fail to be included as a case. In a recent study of clinical examination behaviour in practice, Robinson and colleagues (2014) reported that only 59% of dogs received a full clinical examination and a further 33% had focused clinical examinations only, suggesting thoracic auscultation may not always be routinely performed. As such, especially where there appear to be minimal clinical signs of cardiac disease, thoracic auscultation may be less likely to be performed and the prevalence of disease, possible cases in particular, may have been underestimated. Equally, individuals with heart murmurs due to other causes could have been misclassified as possible cases, as a definitive diagnosis of DMVD requires echocardiographic confirmation (Borgarelli

& Buchanan, 2012). Further, based on the case definition, if excludable criteria were detected by the veterinary surgeon but not recorded in the clinical records, these dogs would have been misclassified as cases. However, the presence of a left apical systolic heart murmur in a dog of typical signalment is highly suggestive of DMVD (Borgarelli & Haggstrom, 2010). Further, the breed, age and bodyweight distributions of possible and diagnosed cases were similar, suggesting that most of the possible cases were as likely to have DMVD as those diagnosed by the attending veterinarian. Nonetheless, the prevalences reported must remain estimates at best, of the frequency of DMVD in dogs presenting to veterinary practices. Secondly, the current study evaluated only factors associated with hazard of death for all-cause mortality. However, within the all-cause mortality group, based on the pre-study power calculations, the number of cases identified substantially exceeded the calculation requirements, suggesting the study had ample power to detect biologically meaningful associations with hazard ratios of 2 or above. A higher powered study evaluating both all-cause and cardiac related mortality, notwithstanding the additional resources implications of reviewing an expanded body of clinical records, could help further elucidate the identified associations. Finally, it is important to acknowledge that the current study was of a convenience sample of corporate and independently owned, exclusively companion animal veterinary practices. Nonetheless, data were from just under 100 practices distributed across England (approximately 2% of RCVS registered veterinary practices), so the main conclusions are likely to be relevant for the practice-attending dog population in the UK.

In summary, this study has highlighted a high prevalence of heart murmurs consistent with DMVD in primary-care practices in England, with DVMD diagnosed less frequently. Survival following detection appeared good for both possible and diagnosed cases, although purebreds, larger and older dogs tended to have a less favourable prognosis. Further studies evaluating

cardiac related mortality and the predictive value of other factors including clinical and biochemical variables in primary-care practice are warranted.

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473 Figures

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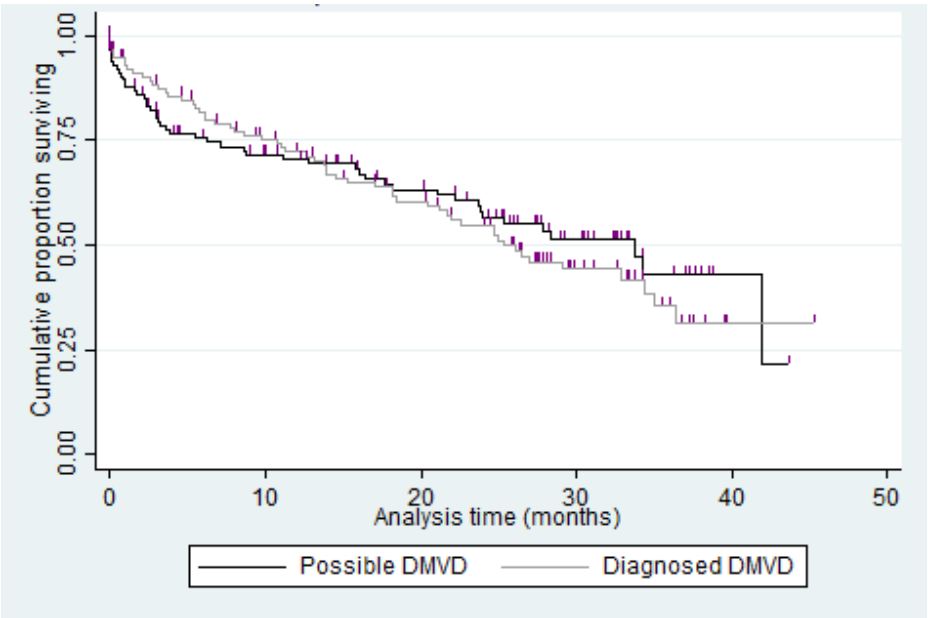

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476 Fig. 1 Kaplan-Meier survival curve of all-cause mortality in incident cases of diagnosed and
477 possible degenerative mitral valve disease in dogs attending primary-care practices in
478 England. Survival time represents the time from when the disease was initially detected until
479 the time of death due to all-cause mortality.

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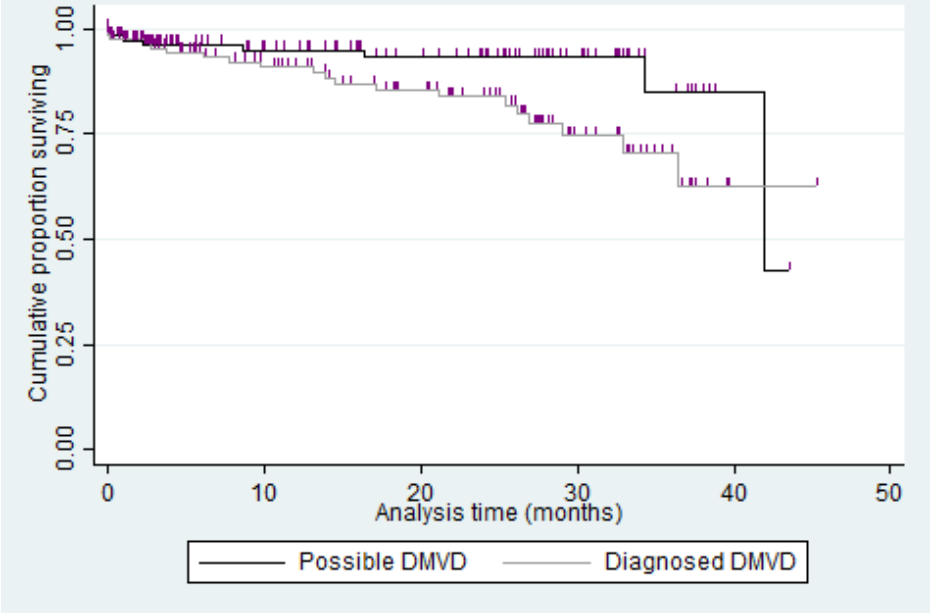

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482 Fig. 2 Kaplan-Meier survival curve of cardiac death in incident cases of diagnosed and
483 possible degenerative mitral valve disease in dogs attending primary-care practices in
484 England. Survival time represents the time from when the disease was initially detected until
485 the time of death due to cardiac disease. Deaths due to other causes were censored.

486

Tables

Table 1. Mean age at diagnosis and survival characteristics of incident cases of diagnosed and a random sample of possible degenerative mitral valve disease in dogs attending primary-care practices in the UK

	Diagnosed DMVD	Possible DMVD[a]
Incident cases, number (%)	116 (28.6)	121 (29.7)
Mean age in years at DMVD diagnosis / murmur detection (standard deviation)	9.52 (3.20)	9.73 (4.01)
All-cause mortality		
Deaths, number (%)	58 (50.0)	49 (40.5)
Median survival time in months (95% CI)	25.4 (20.4 – 34.4)	33.8 (23.7 – 43.1)
Cumulative proportion surviving at 1 year (95% CI)	0.72 (0.64 – 0.80)	0.71 (0.62 – 0.79)
Cumulative proportion surviving at 2 years (95% CI)	0.55 (0.45 – 0.65)	0.57 (0.47 – 0.67)
Cardiac related death		
Cardiac deaths, number (%)	20 (17.2)	8 (6.6)
Median survival time in months (95% CI)	n/a	42.0 (31.2 – 52.7)
Cumulative proportion surviving at 1 year (95% CI)	0.91 (0.85 – 0.97)	0.95 (0.91 – 0.99)
Cumulative proportion surviving at 2 years (95% CI)	0.84 (0.76 – 0.91)	0.93 (0.88 – 0.99)

[a] Possible DMVD cases were defined as dogs over one year old with a documented heart murmur consistent with a diagnosis of DMVD without a specific cardiac diagnosis

Table 2. Descriptive statistics and univariable Cox regression analysis for risk factor association with death (all-cause mortality) among 237 incident cases with diagnosed or possible degenerative mitral valve disease attending primary-care veterinary practices. (Some variables had missing data, e.g. insurance status and bodyweight).

Variable	Number (%)	Hazard ratio	95% confidence interval	P-value
Breed				0.083
Crossbred	43 (18.1)	Baseline	~	
Cavalier King Charles Spaniel	31 (13.1)	0.44	0.21 – 0.96	
Purebred other	163 (68.8)	0.82	0.52 – 1.32	
Sex				0.403
Female	111 (46.8)	Baseline	~	
Male	126 (53.2)	0.85	0.58 – 1.24	
Insurance status				0.940
Not insured	88 (38.8)	Baseline	~	
Insured	139 (61.2)	0.98	0.65 – 1.49	
Maximum bodyweight				0.004
<20.0 kg	163 (72.4)	Baseline	~	
≥20.0 kg	62 (27.6)	1.87	1.24 – 2.83	
Age group (years)				<0.0001
<5.0 years	27 (11.4)	Baseline	~	
5.0 - <10.0 years	97 (40.9)	2.80[a]	2.09 – 3.75	
10.0 - <15.0 years	99 (41.8)			
≥ 15.0 years	14 (5.9)			
Level of diagnosis				0.631
Possible DMVD	121 (51.1)	Baseline	~	
Diagnosed DMVD	116 (48.9)	1.10	0.75 – 1.61	

[a] Hazard ratio relates to each 5 year increment in age

Table 3. Multivariable Cox regression analysis for risk factor association with death (all-cause mortality) among incident cases with diagnosed or possible degenerative mitral valve disease attending primary-care veterinary practices. Observations from 225 of the 237 incident cases (12 had a missing value for one of the final model variables).

Variable	Hazard ratio	95% confidence interval	P-value
Breed			0.053
Crossbred	Baseline	~	
Cavalier King Charles Spaniel	2.78	1.05 – 7.36	
Purebred other	1.86	1.07 – 3.23	
Maximum bodyweight			0.0001
<20.0 kg	Baseline	~	
≥20.0 kg	2.81	1.72 – 4.59	
Age group (years)			<0.0001
<5.0 years	Baseline	~	
5.0 - <10.0 years	3.85[a]	2.61 – 5.69	
10.0 - <15.0 years			
≥ 15.0 years			
Level of diagnosis			0.609
Possible DMVD	Baseline	~	
Diagnosed DMVD	1.12	0.72 – 1.73	
Veterinary clinic (included as a shared frailty term)			0.027
Theta	0.23		

[a] Hazard ratio relates to each 5 year increment in age