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The effect of radiological hip dysplasia and breed on survival in a prospective cohort study of four large dog breeds followed over a 10 year period

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ABSTRACT

The aim of the study was to measure the effect of radiological hip and elbow dysplasia status and breed on overall survival in a cohort of four large dog breeds in Norway. Privately owned dogs of the Newfoundland (NF), Labrador Retriever (LR), Leonberger (LEO), and Irish Wolfhound (IW) breeds were followed prospectively from birth to 10 years of age. The age of death/euthanasia was registered. A total of 501 dogs from 103 litters were enrolled. Kaplan–Meier survival curves were used to describe breed differences in survival times. The effects of radiological hip and elbow dysplasia status as well as breed were assessed using a Cox proportional hazards model. The variables 'sex' and 'living region' were explored as potential confounders.

Among LRs, 60.2% of the dogs were still alive at 10 years of age, and the corresponding figures for NFs, LEOs, and IWs were 28.8%, 16.11%, and 6.4%, respectively. Radiological hip dysplasia status and breed were found to influence overall survival. Two different time-varying effects were observed in that with the IW the hazard of death increased linearly through time, while the effect of severe radiological hip dysplasia decreased logarithmically with time. Location influenced the death hazard and dogs living in suburban areas or cities had longer mean time to death and a lower hazard compared to dogs living in the countryside. Radiological elbow dysplasia status was not found to have an effect on overall survival.

Introduction

Age pattern of survival differs between dog breeds, and large and giant breeds are often reported to have shorter life span than small and miniature breeds indicating that different breeds of dogs age at different speeds (Michell, 1999; Egenvall et al., 2000, 2005; Proschowsky et al., 2003; Adams et al., 2010; Fleming et al., 2011). A Norwegian dog census of Bernese Mountain Dogs, Boxers, and Bichon Frisés found similar aging patterns (Moe et al., 2001).

Canine hip dysplasia (HD) is a frequently occurring skeletal developmental disease, which is probably more prevalent in large breeds, and the occurrence is also influenced by environmental factors (see review by Ginja et al. (2010)). Musculoskeletal diseases are common reasons for euthanasia in large dog breeds (Bonnett et al., 1997; Moore et al., 2001; Fleming et al., 2011) and euthanasia due to HD has been associated with several breeds of dogs (Bonnett et al., 1997; Proschowsky et al., 2003; Malm et al., 2010; Adams et al., 2010).

Many studies on life span and causes of death in dogs have been retrospective and used veterinary teaching hospital populations, records from pet insurance companies, or surveys based on membership of kennel or breed clubs (Bonnett et al., 1997; Michell, 1999; Proschowsky et al., 2003; Egenvall et al., 2005; Fleming et al., 2011). These studies do not address the longevity and cause of death in a general dog population as they have inherent sampling and recall biases (van Hagen et al., 2005; Adams et al., 2010). In the current study, a cohort of privately owned dogs from four large breeds was followed from birth until death or 10 years of age. The aim was to measure if radiological HD and elbow dysplasia (ED) status and breed influenced time to death irrespective of the reported main cause of death.

Materials and methods

Study design

The study was carried out in agreement with the provisions enforced by the National Animal Research Authority (Protocol approval number 05/591-GC).

The work reported here is part of a larger prospective cohort study (the 'main study') aimed at investigating the effects of risk factors on the occurrence of four skeletal diseases (osteosarcoma, panosteitis, HD and ED). The main study included privately owned dogs from four large breeds: Newfoundland (NF), Labrador Retriever (LR), Leonberger (LEO) and Irish Wolfhound (IW) followed from birth and throughout their lives (Trangerud, 2008). A prospective single cohort study was conducted to study to which extent certain factors influence overall survival among dogs from the main study.

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Inclusion

The initial sampling procedure and inclusion of dogs has been previously described (Krontveit et al., 2010). Puppies born in Norway between November 1998 and June 2001 were eligible for inclusion in the main study. All geographical areas of Norway were represented. The breeding stock consisted of dogs born in Norway as well as dogs that had been imported, and inclusion of a litter began when the bitch was mated. All puppies were registered with the Norwegian Kennel Club (NKK).

Not all enrolled dogs continued to completion (Trangerud et al., 2007). In total, 647 dogs from 106 litters from the main study were potentially eligible for inclusion in the present study, which was a convenience sample consisting of 23.2% of the total number of litters born in the included breeds during the period 1998–2001.

The owners of the dogs in the main study were encouraged to have their dog radiologically screened for HD and ED. Radiological HD and ED status were graded by and registered in NKK or in the Swedish ($n = 8$) or Danish ($n = 2$) Kennel Clubs. The inclusion criteria for the single-cohort study were that the dogs were radiologically screened for HD at the official NKK ages, namely 12 (LR, IW) or 18 months of age (NF, LEO). Dogs that were radiologically examined before ages 12 or 18 months (due to clinical signs of hip disease) were included if their hip radiographs were assessed by the NKK panellist.

Questionnaires

Information about the dogs was obtained from the breeder of the litter, the owner of the dog, and the veterinarian examining the dog. Each breeder, dog owner, and veterinarian participating in the project signed a written agreement confirming cooperation and consent. Only information from owners and veterinarians was used in this study and both sources completed questionnaires and recorded information in a specially prepared booklet at specific ages, called 'the observational ages', namely, 3, 4, 6, 12, 18, and 24 months of age. Thereafter, annual questionnaires were mailed to the dog owners until death of the dog or the end of the present study period which was when the dog was 10 years of age.

Not all dogs enrolled continued to completion or filled in all questionnaires, and a few owners did not receive the booklet. Reasons for dropouts included (but were not limited to) the death of the dog, relocation of the owners during the study, and export of dogs abroad (Trangerud et al., 2007).

Outcome variable

Dog owners and veterinarians reported information on the health of the dogs at the observational ages and dates of death/euthanasia were recorded. The owners continued to report on the annual questionnaires at the approximate ages of 3, 4, 5, 6, 7, 8, 9, and 10 years. Participants who did not respond for various reasons were contacted by telephone, and the age of death/euthanasia was registered. Factors related to the dog and the owner as well as the veterinarian examining the dog influence decisions regarding euthanasia (Yeates and Main, 2011) so the endpoint in the analysis was defined as euthanasia or death irrespective of the reported main cause and the outcome is simply referred to as 'death'.

Cases lost to follow-up or still alive at the end of the study were included in the survival analysis up to the last time point at which they were known to be alive and were thereafter censored. Dogs that died before the age of 3 months were excluded and preliminary analyses showed that no dogs died between the ages of 3 and 6 months. For technical reasons, 6 months were therefore subtracted from the time at risk, and the outcome variable 'time from 6 months to death until 10 years of age' was obtained.

Risk factors

The variables breed, sex (male or female), location (living region), and radiological HD and ED statuses were examined for potential influence on overall survival. The screening procedure for HD for the dogs has been previously described (Krontveit et al., 2010). The Fédération Cynologique Internationale (FCI) grading scale was used with the following measures: A (excellent), B (normal), C (mild dysplasia), D (moderate dysplasia) and E (severe dysplasia) (Fluckiger, 2007). In the analyses the HD status was reclassified into free (A and B), mild (C), moderate (D), and severe (E) and this variable was termed radiological HD status. The International Elbow Working Group (IEWG) elbow protocol[1] was used for grading of elbow radiographs into the grades free, mild, moderate, and severe. This variable was termed radiological ED status.

The location (or living region) of the owner was categorized as countryside, suburban, or city, based on the owner questionnaires. Preliminary analysis showed very few observations in the city category, so city and suburban were merged into a single category.

[1] International Elbow Working Group, 2001. International Elbow Protocol (Vancouver). http://www.iewg-vet.org/archive/protocol.htm (accessed 15 March 2011).

Statistical analyses

Stata 11 (Stata Corporation) was used for all analyses. The distribution of dogs by breed, sex, radiological HD and ED status, and living region was calculated. The number and percentage of deaths, mean time to death or censoring, and total number of subjects in each category of the variables were calculated. Kaplan–Meier survival curves were used to describe breed differences in survival times and to estimate median survival time. Separate Kaplan–Meier curves for each breed and by radiological HD status were used to evaluate the effect of radiological HD status on survival in each of the breeds.

A Cox proportional hazards model was applied to estimate the effect of possible risk factors on 'time to death', and 'time at risk' was measured in months from 6 months to death or censoring or 10 years (120 months). The dogs were clustered into litters. The assumption of independence between observations was therefore violated and a shared frailty term for 'litter' was included in the model. The Efron approximate method was used to handle ties (Dohoo et al., 2009). Collinearity between all variables was evaluated by Goodman and Kruskal's gamma (γ) for ordinal or dichotomous variables and by the phi (φ) coefficient for nominal variables.

A multivariable Cox proportional hazard model with shared frailty for litter was constructed using manual forward selection by offering the variables one at a time. Predictors were retained in the model when the probability (P) of the likelihood ratio test (LRT) was <0.05. Potential confounding and intervening variables were evaluated after initially constructing a causal diagram. Changes of >20% in the coefficients in the model with the potential confounder present were also used as indication of confounding. A variable was considered to be intervening if adding it substantially altered the effect of a factor and if the intervening variable lay on the causal path between the factor and the outcome. Interactions between significant predictors in the model were tested by adding an interaction term. To specifically evaluate the relationship between radiological HD and ED status an interaction term between these two variables was also added to the model. Interaction terms were retained if $P < 0.01$ as judged by the LRT. Following forward selection the model was built again using backward elimination. The LRT was used to evaluate the significance of the categorical predictors in the final model. The significance of the shared frailty term was evaluated through a LRT. An estimate of the baseline hazard was derived conditional upon the set of coefficients in the model.

Validation of the model

The assumption of proportional hazards was evaluated using the test for proportional hazards based on the Schoenfeld residuals for each variable in the model. If there was violation of the proportional hazards assumption and graphical assessment indicated a time-varying effect (TVE) of a variable, an interaction term between the variable and time (on either a linear or logarithmic scale) was included in the model. The assumption of independent censoring was evaluated by sensitivity analyses based on both complete positive and complete negative correlation between censoring and outcome. The amount of explained variation was evaluated by an overall r^2 statistic for proportional hazard models. Plots of the deviance residuals, score residuals, and scaled score residuals against time at risk were used to identify outlying observations with influence on the model, and the model was fit with and without any outlying observations (Dohoo et al., 2009).

Results

Descriptive statistics

The number of deaths, mean time to death or censoring, and total number of subjects in each category of the variables investigated are provided in Table 1. Of the 501 dogs included, 73 were lost to follow up some time during the observation period, 149 were still alive at the end of the study, and 279 dogs died. Fig. 1 shows the Kaplan–Meier survival curves by breed and indicates that >50% of LRs were alive at 10 years of age. The median survival time was 7.3 years for NF and 7 years for both LEO and IW. Among LR, 60.2% were still alive at 10 years of age, and corresponding figures for NF, LEO, and IW were 28.8%, 16.11% and 6.4%, respectively.

Fig. 2a and c indicates that severe radiological HD status had the greatest effect on survival before 2 years of age in NF and LEO, while moderate radiological HD status had a great effect in IW (Fig. 2d).

Survival analysis

Collinearity was not detected between any of the variables. Both forward selection and backward elimination resulted in the