TITLE: Incidence and risk factors for the diagnosis of lymphoma in dogs in UK primary-care practice

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Abstract

Objectives

Canine lymphoma is one of the most commonly encountered neoplasms in veterinary medicine. This study aimed to identify the incidence, risk factors and presenting signs of lymphoma in dogs presenting to primary-care practice in the United Kingdom using analysis of primary-care data within the VetCompass™ programme.

Methods

Case records from the VetCompass™ programme from primary-care practices in the UK were searched for newly diagnosed canine lymphoma cases within a one-year period, 2013. Diagnosis was based on clinical records with or without laboratory confirmation. Signalment was evaluated as risk factors for lymphoma diagnosis using multivariable logistic regression.

Results

There were 286 presumed newly-diagnosed cases identified during 2013 from 455,553 dogs (overall incidence risk 63/ 100,000 dogs/ year) of which 193 (67%) were laboratory confirmed (lab-confirmed incidence 42/ 100,000 dogs/ year). Advanced age; dogs older than 12 years, bodyweight; dogs greater than 30kg, and breed were significantly associated with lymphoma diagnosis. Only 18 dogs (6%) of the population identified were referred to a referral centre.

Clinical Significance

The incidence of canine lymphoma reported in this study is similar to that reported in previous studies looking at different populations of dogs. This study agrees with previous studies that age, bodyweight and breed are significant risk factors for lymphoma. Results of this study highlight the low number of cases with canine lymphoma referred within the population of the United Kingdom, emphasising the importance of research programmes like VetCompass™ to evaluate diseases in the wider general population.

Keywords

VetCompass, lymphoma, lymphosarcoma, first opinion, breed-associated risks, canine, dog

Abbreviations

CI – confidence interval

EPR – electronic practice record

IQR – interquartile range

OR – odds ratio

PARR – PCR for antigen receptor rearrangements

XXX - XXXX XXXXX XXXX

SD - standard deviation

UK – United Kingdom

LRT - likelihood ratio test

Introduction

Lymphoma is the most common malignant neoplasm of the canine haemopoetic system and is the most frequently medically-managed neoplasia in veterinary oncology (Zandvliet, 2016). Lymphoma is a general term that represents several different distinct forms of neoplastic lymphoid cells, many of which have been characterised based on anatomic location, histopathological appearance and immunophenotype (Valli, et al., 2013). The clinical presentation, molecular characteristics, treatment and response to treatment of canine multicentric lymphoma is similar to that reported for non-Hodgkin's lymphoma in humans (Zandvliet, 2016). This makes lymphoma in dogs an attractive translational spontaneous model for study of lymphoma in humans.

Previous studies have documented an incidence of between 7 to 107 cases per 100,000 dogs per year depending on the population of dogs being observed: either insured dogs or extrapolated from samples submitted to a pathology laboratory (Edwards, et al., 2003; Pastor, et al., 2009). In a questionnaire-based study examining cases presenting to primary-care practice within the UK, this number increased slightly to 122 cases per 100,000 dogs per year (Mellanby, et al., 2002).

The incidence of canine lymphoma has been associated with increasing age with the most common occurrence in middle aged to older dogs (~6-9 years) (Edwards, et al., 2003). A more recent study of Australian dogs reported increased risk of diagnosing lymphoma in dogs over the age of 7 years (Yau, et al., 2017).

Whilst sex and neutering status have not traditionally been associated with increased risk of lymphoma diagnosis, recent reports did find entire animals, particularly entire females under-represented within the populations of animals studied. (Belanger, et al., 2017; Yau, et al., 2017).

Breed has been identified as a risk factor for diagnosis of naïve (not previously treated) lymphoma in dogs. Boxers, British bulldogs and bull mastiffs have all been reported with higher incidence of lymphoma (Edwards, et al., 2003), Australian cattle dogs, rottweilers and Doberman pinschers have also been reported at increased risk (Yau, et al., 2017). Golden retrievers were reported at increased risk in another study which also identified breed as a risk factor for diagnosis of lymphoma. This study also looked at immunophenotype and recorded that cocker spaniels and basset hounds appeared predisposed to B cell lymphoma whilst shih-tzus and Siberian huskys appeared at an increased risk of T cell lymphoma (Modiano, et al., 2005). The significance of this is important as immunophenotype has been reported as an important prognostic variable in canine lymphoma (Dobson, et al., 2001).

Recent phylogenetic mapping of the canine genome (von Holdt, et al., 2010) has allowed greater understanding of the domestication of dogs and may provide a useful framework within which "at risk" breeds can be associated for further genetic analysis. A more recent analysis focussing on breed associated risk for diagnosis of lymphoma has identified different "at risk" breeds depending on the European country of origin (Comazzi, et al., 2018).

Mellanby et al. (2002) reported that the most commonly used tests to diagnose lymphoma in primary-care practice in the UK were fine needle aspiration (FNA) or biopsy of peripheral lymph nodes. Within this study it was reported that often both tests were performed. Following diagnosis, the majority of these animals were reported as receiving some type of treatment for their lymphoma. When looking at the number of dogs referred, 68% of the primary-care clinicians had never referred a dog with lymphoma (Mellanby, et al., 2002).

This present study had 3 main objectives; (1) to estimate the incidence of lymphoma in dogs presenting to primary-care practice, (2) describe presenting signs and clinical investigations performed and (3) to identify risk factors for diagnosis of lymphoma in dogs within this primary-care population.

Materials and Methods

The study included a retrospective cohort of all dogs attending an available subset of VetCompass™ participating practices during 2013 (Vet Compass, 2017). Anonymised electronic patient records (EPR) were included from dogs under primary veterinary care between January and December 2013. Ethics approval was provided by the XXXX XXXX XXXX's Ethics and Welfare Committee (XXXXX) and the XXXXX XX XXXXX's Ethics and Welfare Committee (XXXXXX).

Potential cases were identified from the electronic database by searching for terms associated with lymphoma within the clinical notes (lympho*, lymphoma, lymphosarcoma, LSA, B-cell, T-cell and Immunophenotype) and treatments (vinc*, doxo*, cyclop* and lomust*). The full clinical records of these potential cases were then manually assessed by a single assessor to confirm whether they met the inclusion criteria.

Cases were included for the study if; the attending clinician had made a diagnosis of lymphoma based on history and clinical signs, with or without laboratory confirmation. A sub-group was identified that had a laboratory diagnosis. Cases were included if lymphoma had been diagnosed using cytology from fine needle aspirates, histopathology of biopsies or using the Canine Lymphoma Blood test (Avacta). Cases were excluded from analysis if: i) they had been diagnosed with lymphoma prior to January 2013, ii) if a diagnosis of leukaemia could not be excluded within the laboratory confirmed group and/or iii) if a case was reported as being seen at a practice as a second opinion. All dogs within the year assessed that were not identified as potential lymphoma cases based on the search terms were included in the analysis as non-cases.

From included cases, data on the diagnostic tests undertaken, clinical signs and anatomical location of lymphoma were all extracted from the EPRs based on either automatic recording by database software or following manual assessment from the clinical records, and descriptive analysis performed. Clinical notes were assessed as to whether dogs were recorded as hypercalcaemic, defined as a total or ionised calcium greater than the reference range, at presentation. Whether the case was referred for advanced clinical management of lymphoma was also noted as part of the study.

Breeds were categorised as a variable using VeNom standardised breed terms (VeNom coding group, 2017). Purebreeds were grouped into types as defined by the Kennel Club (Kennel Club, 2017). Any dog that was classified as a breed cross or a designer breed was classified as a "crossbreed". A designer breed incorporated a cross breed with a standard name (e.g. lurcher). Pure and designer breeds were identified individually where 3 or more dogs of that breed had been included as cases. Pure breeds with less than 3 dogs included were grouped as "other". Sex and neuter status were included in the risk analysis with male neutered dogs used as the baseline for risk analysis. Both sex and neuter status were included in the univariable analysis due to the interest in neuter association on its own and with the potential interaction between sex and neuter status. Age and weight were analysed initially as continuous variables but no linear association was present and so were analysed as categorised variables. The age (years) at first diagnosis of lymphoma was calculated and categorised into 4 groups, formulated around the reported median age of diagnosis based on previously published literature (Yau et al., 2017, Dobson et al., 2001, Edwards et al., Pastor et al., 2009): < 5, 5 to < 8, 8 to < 12 and ≥ 12 years. Dogs with ages of < 5 years were used as the baseline value for risk factor analysis. Maximum recorded bodyweight (kg) during 2013 was categorised into 4 groups: < 10, 10 - < 20, 20 - < 30 and ≥ 30 for ease of analysis. Any missing values were included into an additional unknown group. Dogs in the 10 - < 20 kg groups were used as the baseline for risk factor analysis to reflect the category with the median bodyweight of the reference population.

All data were exported to a spreadsheet, cleaned and duplicates removed in Excel (Microsoft Corp.) before transferring into Stata Version 13.1 for analysis (Stata Corp.). Descriptive statistics were generated for the case and non-case dogs within the study population. Quantitative data were assessed graphically for normality and summarised with the median (interquartile range, IQR) or mean (standard deviation, SD). Categorical data were summarised with number (%).

Annual incidence risk with 95% confidence intervals (CI) was estimated by calculating the proportion of incident cases within the total study cohort that were under veterinary care during 2013 (n=455,553). Specific breed incidences were also estimated by calculating the proportion of incident cases of a specific breed within the total study population of the same breed. The CI estimates were derived from standard errors based on approximation to the normal distribution (Kirkwood & Sterne, 2003).

Logistic regression modelling was used to identify potential risk factors associated with a diagnosis of lymphoma with separate models created for all cases and also for those cases with a confirmed laboratory diagnosis. In the univariable analysis, variables with a likelihood ratio test (LRT) of $p < 0.20$ were carried forward to the multivariable model. A forward stepwise manual approach was used to build the multivariable model to find the variables associated with a diagnosis of lymphoma ($P<0.05$). A 20% change in the odds ratio when the subsequent variable was added to the model was used to identify potentially confounding variables (Dohoo et al, 2010). Assessment for multicollinear variables was achieved by checking that two variables have a correlation coefficient $r <0.08$ as well as looking at the size of the standard errors and confidence intervals of the variable coefficients (Katz, 2011). Only one variable would be included into the multivariable model in the situation of multicollinearity. Plausible interactions were examined with the likelihood test of

homogeneity. Age and weight were assessed for linearity using the likelihood ratio test for departure from trend and likelihood ratio test for extra-linear effect. Model fit was assessed both with the Hosmer-Lemeshow test and calculating the area under the ROC curve (Hosmer Jr, et al., 2013). Statistical significance was set at $p < 0.05$.

Multiple a priori sample size calculations were performed to ensure adequate power for each study aim. For incidence estimation, an analysis required 54,000 dogs to estimate the incidence risk of lymphoma in UK dogs with an expected frequency of 100/100,000 dogs per year and a margin of error of 0.01%. It was also estimated a study with 2,150 dogs of a specific breed accounting for 1% of the denominator study population and 40,880 crossbred dogs would be required to detect breed as a risk factor of being diagnosed with lymphoma, with odds ratio of 2.0 or greater (80% power and 95% confidence). (Centers for Disease Control and Prevention (US), 2017).

Results

The study population consisted of 455,553 dogs under care at 34 veterinary clinics across the UK. There were 1,991 potential cases identified for manual review; 286 dogs were identified with a clinical presentation most consistent with lymphoma of which 193 dogs had a laboratory confirmed diagnosis. The annual incidence risk was estimated as 63/100,000 dogs per year (95% CI 55.72-70.49) overall with an incidence of 42/100,000 dogs per year (95% CI 36.60-48.78) estimated in laboratory confirmed cases.

For dogs with a laboratory confirmed diagnosis, diagnosis was made by cytology following FNA in 123 (64%) cases, 73 (38%) had a biopsy and 10 (5 %) had a diagnosis based on the Canine Lymphoma Blood Test (CLBT) (Avacta). Some dogs had more than one laboratory test performed to establish a diagnosis. When considering staging modalities used, forty-one (14%) dogs had radiography performed as part of their investigations and 42 dogs (15%) had ultrasound performed. One doghad a bone marrow biopsy (*Figure 1)*.

The most common anatomical form of lymphoma was multicentric with 233 (83%) of cases overall and 144 cases (78%) of the laboratory confirmed cases. The next largest anatomical form within the laboratory confirmed group were the cutaneous form with 18 cases (9%) and the alimentary form with 10 cases (6%). Thirty-nine (13%) cases had immunohistochemistry with one case immunophenotyped using PARR, 22 cases (56%) were diagnosed with B cell lymphoma and 17 cases (44%) with T cell lymphoma. Of these there were 19 multicentric B cell lymphomas reported and 3 multicentric T cell lymphomas. All cutaneous forms that had immunohistochemistry were T cell lymphomas (n=9). The two mediastinal lymphomas that were immunophenotyped were B cell. Both of the alimentary lymphomas that were immunophenotyped were T cell. The case immunophenotyped using PARR was reported as an indolent alimentary lymphoma. Twenty-two cases of the 73 cases diagnosed following a biopsy (30%) had records relating to tumour grade. Of these 16 (73%) were described as high grade or large cell and 6 (27%) were described as low grade, small cell or indolent.

Overall, the most common presenting sign, as recorded in the clinical notes, was lymphadenopathy with 236 dogs presenting with lymphadenopathy (83%). This was followed by lethargy in 94 dogs (33%), weight loss in 47 dogs (16%), hyporexia/anorexia in 46 dogs

(16%), vomiting in 37 dogs (13%), polyuria and/or polydipsia in 31 dogs (11%) and coughing present in 28 dogs (10%). Only 17 cases (6%) were documented as being hypercalcaemic. The majority of cases presented with a combination of clinical signs but no dominant combination was present on subjective analysis of the data.

Median age overall at diagnosis was 9 years (IQR 7-12) with a younger median age of 8 years (IQR 6-11) in those with a laboratory confirmed diagnosis. 127 (44%) of the dogs with lymphoma were female and 158 (56%) were male, of which 80 (63%) and 81 (51%) respectively were neutered at the time of diagnosis. In those with a laboratory confirmed diagnosis 87 (45%) were female and 112 (58%) of those were neutered. Eighteen cases (6%) were noted as being referred based on manual assessment of clinical records. One hundred and eighteen dogs (41%) were euthanized following diagnosis without further treatment, 104 dogs (36%) were treated with palliative prednisolone and 55 dogs (19%) received chemotherapy. Fifteen out of the 18 cases referred were treated with chemotherapy and of these nine received a CHOP based protocol.

Individual breeds with the highest incidence risk of lymphoma included Scottish terriers (436/100,000 dogs per year, 95% CI 119-1113), dogue de Bordeaux (272/100,000 per year, 95% CI 88-633), bull terriers (256/100,000 per year, 95% CI 83 - 596) and boxers (242/100,000 per year, 95% CI 136 - 399) (see *Table 1)*.

Univariable analysis identified age, neutering status, bodyweight and breed all being strongly associated with increased risk of diagnosing lymphoma overall. Dogs aged ≥ 12 years had the highest odds of developing lymphoma when compared to the baseline (OR 11.74, 95% CI 7.81-17.65). Neutered dogs had increased odds of being diagnosed with lymphoma compared to those that were entire (OR 1.92, 95% CI 1.46-2.53) with entire females having the lowest odds (0.28, 95% CI 0.15-0.51). Heavier dogs (≥ 30kg) had increased odds of being diagnosed with lymphoma than those between 10 - < 20kg (OR 1.54 95% CI 1.14-2.01). Overall increased odds were observed for Scottish terriers, bull terriers, boxers, dogue de Bordeaux, lurchers and West Highland white terriers, rottweilers and golden retrievers (*Table 2)* The Kennel Club group with the highest odds for a diagnosis was the working group (OR 2.07 95% CI 1.39-3.08).

Age, breed and bodyweight were included in the multivariable analyses. Increasing odds were observed in increasing age groups. Overall, the highest risk group was found to be the oldest age group (≥ 12 years of age) with over 10 times the odds compared to the youngest age group (OR 10.20, 95% CI 6.72-15.48). Odds of lymphoma increased with increasing bodyweight with the heaviest group (≥ 30kg) having an increased odds of lymphoma compared to the baseline 10-20kg group (OR 1.56, 95% CI 1.06-2.30). No linear or extra-linear association of age or weight were found. There were no interactions or multicollinearity between variables. Scottish terriers, dogue de Bordeaux, bull terriers, West Highland white terriers and boxers all had increased odds of diagnosis of lymphoma when compared to crossbred dogs (*Table 3)*. Additionally, when looking at the laboratory confirmed cases, schnauzers that previously had a non-significant increased odds ratio became significantly at risk. The associations of sex and neuter status with lymphoma were confounded by age. After accounting for age, these two variables were no longer statistically significant and were

therefore were not retained in the multivariable model. Age was retained in the model as the confounder and variable of interest. No further confounders were identified.

Discussion

The study aimed to apply inclusion criteria to reflect as closely as possible the epidemiological picture of canine lymphoma as it presents and is recorded in primary-care practice in the UK assuming that many cases may not be fully clinically investigated and that the decision to euthanize may often be made based heavily on clinical signs. The overall incidence of 63/ 100,000 dogs per year falls within the range previously reported for canine lymphoma with an incidence of between 7-122/ 100,000 dogs per year (Edwards, et al., 2003; Pastor, et al., 2009; Mellanby, et al., 2002). This number drops but not excessively to 42/ 100,000 dogs per year when considering the laboratory confirmed cases. The most common presenting clinical signs are similar to those previously reported; lymphadenopathy, lethargy, weight loss, anorexia (Zandvliet, 2016).

The VetCompass™ programme allows for analysis of clinical records for epidemiological studies that aim to reduce selection and reporting biases that limit other study designs based on questionaires, referral data and cancer registries (O'Neill, et al., 2014). The benefit of using this method to collect and analyse data is to reduce potential bias that may be implicit when sending out questionaires, such as Mellanby et al (2002),. This study sent out questionaires to 1000 randomly selected first opinion practices. This method, like the one used in our study, eliminated the bias of selecting only practices that usually refer dogs with lymphoma to referral centres. However this cannot limit the bias that can be caused by the population described by responders to the questionaire versus those who do not respond.

The most common anatomical presentation of lymphoma identifed in this study was multicentric. The high proportion (83%) of cases presenting with multicentric lymphoma, whilst to be expected given the reported prevalence of this type of lymphoma (Zandvliet, 2016), also can reflect some of the limitations of this study. The anatomical classification was reliant either on the veterinary surgeon recording the diagnosis within the clinical notes or based on the assessor's interpretation of the clinical records. Inconsistencies within the clinical notes or the lack of further investigations meant that some other anatomical forms of lymphoma may have been missed or misclassified.

The types of diagnostic and staging investigations used to confirm a diagnosis of lymphoma were similar to those previously reported by Mellanby et al (2002). Fine needle aspiration (63%) and biopsies (38%) were the most commonly used modalities. Only 41 (14%) dogs had radiography performed and 42 dogs (15%) had ultrasonography. Further to this, only 39 (13%) cases had immunophenotyping performed, which is interesting because immunophenotype could inform prognosis as described by Dobson et al. (2001), Marconato et al. (2011) and Rao et al. (2011) and potentially influence selection of treatment protocol. Whilst not directly impacting on risk factors, immunophenotype may be associated with certain types of lymphoma or certain breeds and so may indirectly influence risk for developing the disease (Dobson, et al., 2001). The low numbers of cases that had immunophenotyping may also reflect the number of dogs treated with chemotherapy, as these are the most likely cases to have had immunophenotyping as part of their investigations.

The number of investigations in these cases may reflect the realities of diagnosing and managing canine lymphoma within primary-care practice but also highlights a potential need

for further education of practitioners as to the opportunities and significance of different diagnostics available and their relevance as to prognosis when deciding on appropriate therapy. The number of investigations are likely to be underestimated as investigations carried out at referral practices or other practices were not recorded unless recorded within the clinical text. An example of this is the recording of grade of lymphoma when a biopsy had been performed, this was only available for 30% of the cases assessed. This highlights potentially both a limitation and an observation from this study which is that even following a biopsy there were only a relatively low number of lymphomas (30%) where a grade was reported. This is potentially explained by the lack of recording of lymphoma grade within the clincial notes but possibly highlights another area where further education of primary-care practioners may alter their approach to the diagnosis and classifying of theses lymphomas, especially given the better prognosis that can be seen with some of the more indolent forms of the disease. It is possible now that with the advent of newer molecular techniques available to primary-care practices that this may have changed and that there is now a difference in the investigations carried out within primary-care practice when compared to the time period seen in this study.

Whilst the univariable analysis identified sex and neutering status as associated with an increased risk of developing lymphoma as previously reported by Belanger et al (2017) and Yau et al (2017), these potential risk factors did not reach significance when included in the multivariable analysis in this study, highlighting the continued importance of multivariable analysis in trying to eliminate confounding variables that may have been present in older studies. The multivariable analysis identified age, bodyweight and breed as risk factors within our population for the development of lymphoma: cases older than 12 years were at highest risk, although interestingly, when only laboratory confirmed cases were analysed, the odds reduced to a similar odds ratio to the 8-12 year old group, as reported by Edwards et al (2003) and Yau et al (2017). It is possible that this reflects the increased likelhood of primary-care practioners to consider a diagnosis of lymphoma without laboratory confirmation in older patients. It should be considered that categorisation of age results in the assumption that the effect measure is equal across each category which may not always be the case (Altman et al 2006). However the categories used were intended to represent different general age groups of dogs based on previous studies and to aid the clinical interpretation of the association with age.

The increased risk of lymphoma diagnosis associated with increased bodyweight at diagnosis is interesting. Though breed and bodyweight are likely to be related, they were not found to be highly correlated in analysis and the model remained stable when both were included. The weight variable may be incorporating a size element that is not encompassed by breed and therefore a genetic basis. Increased body mass index whilst young has been shown to be associated with increased risk of developing certain types of lymphoma in later life in humans; including diffuse large B cell lymphoma, the most commonly occuring type of lymphoma reported in dogs (Chihara, et al., 2015). However, this finding may be biased by the type of breed, with some breeds e.g. dogue de Bordeaux and rottweiler naturally being heavier than others. This will always be considered an issue when multiple dog breeds are being included in analysis and represent the phenotypic range of sizes seen in domestic dogs. Whilst individual anlaysis of breeds would allow a more accurate assessment of weight within a single breed and its association with developing lymphoma, it is likely that acquiring the

number of cases to achieve statistical significance would be difficult. It would be interesting in any future studies to look at body condition score as a more accurate risk factor, thereby reducing some of the inherent bias introduced by looking at different breeds. Unfortunately such analysis was beyond the scope of this study.

Previously a number of different breeds have been associated with increased risk of developing lymphoma including boxers, bulldogs, bull mastiffs, rottweilers and golden retrievers (Edwards, et al., 2003; Modiano, et al., 2005; Yau, et al., 2017). Our study also identified increased risk of developing lymphoma in breeds such as bull terriers, Scottish terriers and West Highland white terriers as well as the previously reported breeds. When considering the breed types identified by von Holdt et al. (2010) it is interesting that the breed groups to which the majority of these dogs belong are closely located on the phylogenetic tree. It is possible that further genetic analysis ofgroups could offer insight into the genetic aetiology or predisposition of lymphoma in dogs. However this may be a gross simplification of what is actually an aetiologically diverse and complicated group of diseases which also may have a significant environmental component to the development of the disease. There is the further complication that there are variations in risk associated with different breeds in different countries (Comazzi, et al., 2018).

The retrospective nature of the study meant that there were several incomplete variables that would have potentially added more scope to the risk factor analysis. This combined with the high case numbers needing to be manually assessed means that it is possible staging and other factors indicating a diagnosis of lymphoma may be missed leading to under-reporting of clinical signs or diagnostics performed. It is also possible that the risk factor analysis was underpowered when considering certain breed susceptibility due to the low number of dogs per breed that had a diagnosis of lymphoma, an obvious example of this being the incidence and breed susceptibility of Scottish terriers that had an incidence of 436 with a very wide confidence interval (119-1113) and an odds ratio of 4.78(95% CI 1.72-13.34). This is very likely a reflection of the small number of Scottish terriers recorded in the study (n=4) and highlights the difficulties inherent in this type of study that despite recording a large number of total cases, a single breed analysis can still yield very small numbers, and caution should be used when interpreting the results.

As previously mentioned, body condition score would have probably been a better assessor of the significance of being overweight with respect to the risk of developing lymphoma. Further, it should be noted, maximum body weight was elected as many cases did not have a weight recorded on the date of diagnosis and for non-cases there was not always an equivalent date of diagnosis, such that maximum weight was considered the most consistent measure of comparison. However this type of analysis is always going to be limited by the breadth of information provided in the clincial records and there were large variations in detail and content present within the records analysed. One of the consequences or reflections of this is that this study was looking for cases with “lymphoma.” Given that lymphoma reflects a wide variety of different conditions within the canine population, and often the investigations required to distinguish these conditions can be quite extensive, this study can only ever report on generalities observed. Hopefully this study can add to the evidence base for future studies looking to analyse the epidemiology of canine lymphoma.

There was not an obvious difference in populations between all included cases and the sub-group that had a laboratory confirmed diagnosis, nor was there an observed difference when other studies were subjectively assessed for similarities. This may be an underestimation as cases where referral centres were consulted for advice were not identified within this group andit was not always possible to assess from the clinical notes whether a dog was referred. The incidence, breeds and clinical signs reported were similar to those which have previously been reported. No new at risk breeds were identified overall that were not present in the laboratory confirmed cases. This would indicate that even with the broadest of inclusion criteria, there was not a different, previously unidentified group of dogs within the primary-care population.

Further analysis of outcomes within this same population of dogs would allow further interrogation of the cases identified as it was noted that treatment of these animals did vary. Survival analysis dependent on breed, presenting signs and treatment given would add to the evidence base for primary-care practioners. There are possible genetic links that could be explored further and the breeds identified should have further scrutiny as to the type of lymphoma that they developed.

This study concluded that the incidence of canine lymphoma was 63 cases/ 100,000 dogs per year, with an incidence of laboratory confirmed cases of 42 cases/ 100,000 dogs per year. Age, bodyweight and breed were all considered significantly associated with increased risk of developing lymphoma. The suspected at risk breeds, although there were low numbers of dogs within each individiual breed, following multivariate analysis, were Scottish terriers, dogues de Bordeaux, bull terriers, West Highland white terriers, schnauzers and boxers. These results can, with the previous studies already published, add to the evidence base for primary-care practioners when considering dogs that present with clinical signs consistent with lymphoma.

Conflicts of Interest

No conflicts of interest have been declared

References

Altman D. G., and Royston P., "The cost of dichotomising continuous variables." British Medical Journal (Clinical research ed.) vol. 332, no.7549, pp. 1080, 2006.

Belanger J. M., Bellumori T. P., Bannasch D. L., Famula T. R., and Oberbauer A. M., "Correlation of neuter status and expresison of heritable disorders" Canine Genetics and Epidemiology vol. 4, no 6, 2017.

Centers for Disease Control and Prevention (US), "Introducing Epi info 7," 2017. [Online]. Available: http://wwwm.cdc.gov/epiinfo/7. [Accessed July 2017].

Chihara D., Nastoupil L. J., Williams J. N., Lee P., Koff J. L. and Flowers C. R., "New insights into the epidemiology of non-Hodgkin lymphoma and implications for therapy," Expert Review of Anticancer Therapy, vol. 15, no. 5, pp. 531-544, 2015.

Comazzi S., Marelli S., Cozzi M., Rizzi R., Finotello R., Henriques J., Pastor J., Ponce F., Rohrer-Bley C., Rütgen B. C. and Teske E., "Breed-assocaited risks for developing canine lymphoma differs among countries: an European canine lymphoma network study," BMC Veterinary Research, vol. 14, no. 232, pp. 1-7, 2018.

Dobson J. M., Blackwood L. B., McInnes E. F., Bostock D. E., Nicholls P., Hoather T. M., and Tom B. D., "Prognostic variables in canine multicentric lymphosarcoma," Journal of Small Animal Practice, vol. 42, pp. 377-384, 2001.

Dohoo I.R., Martin W. and Stryhn, H., Veterinary epidemiologic research, Charlottetown, Canada: AVC Incorporated, 2003

Edwards D. S., Henley W. E., Harding E. F., Dobson J. M., and Wood J. L., "Breed incidence of lymphoma in a UK population of insured dogs," Veterinary and Comparative Oncology, vol. 1, no. 4, pp. 200-206, 2003.

Hosmer Jr D. W., Lemeshow S., and Sturdivant R. X., Applied logisitic regression, New York: WIley & Sons, 2013.

Katz M. H., Multivariable Analysis – A Practical Guide for Clinicians and Publich Health Researchers, 3rd edition, Cambridge University Press, 2011

Kennel Club, "Kennel Club UK (online)," 2017. [Online]. Available: http://www.kennelclub.org.uk. [Accessed 2017].

Kirkwood B. R., and Sterne J. A., Essential Medical Statistics, Oxford: Blackwell Science, 2003.

Marcanoto L., Stefanello D., Valenti P., Bonfanti U., Comazzi S., Roccobianca P., Caniattie M., Romanelli G., Massari F., and Zini E., "Predictor of long-term survival in dogs with high-grade multicentric lymphoma." Journal of the American Veterinary Medical Association, vol. 238, no. 5., pp. 480-485, 2011

Mellanby R., Herrtage M. E., and Dobson J. M., “Treatment of canine lymphoma by veterinarians in first opinion practice in England,” Journal of Small Animal Practice, vol. 43, no. 5, pp. 198-202, 2002.

Modiano J. F., Breen M., Burnett R. C., Parker H. G., Inusah S., Thomas R., Avery P. R., Lindblad-Toh K., Ostrander E. A., Cutter G. C., and Avery A. C., “Distinct B-Cell and T-Cell Lymphoproliferative Disease Prevalence among Dog Breeds Indicates Heritable Risk,” Cancer Research, vol. 65, no. 13, pp. 5654-5661, 2005.

O'Neill D. G., Church D. V., McGreevy P. D., Thomson P. C., and Brodbelt D. C., “Approaches to canine health surveillance,” Canine Genetics and Epidemiology, vol. 1, no. 2, 2014.

Pastor M., Chalvet-Monfray K., Marchal T., Keck G., Magnol J. P., Fournel-Fleury C., and Ponce F., “Genetic and Environmental Risk Indicators in Canine Non-Hodgkin’s Lymphomas: Breed Associations and Geographic Distribution of 608 Cases Diagnosed throughout France over 1 Year,” Journal of Veterinary Internal Medicine, vol. 23, no. 2, pp. 301-310, 2009.

Rao S., Lana S., Eickhoff J., Marcus E., Avery P. R., Morley P. S., and Avery A. C., “Class II major histocompatibility complex expression and cell size independently predict survival in canine B-cell lymphoma.” Journal of Veterinary Internal Medicine vol. 25, no. 5, pp. 1097-1105, 2011.

Valli V. E., Kass P. H., San Myint M., and Scott F., “Canine lymphomas: association of classifcation type, disease stage, tumour subtype, mitotic rate, and treatment with survival,” Veterinary Pathology, vol. 50, no. 5, pp. 738-748, 2013.

VeNom coding group, “Venom Veterinary Nomenclature,” 2017. [Online]. Available: http://venomcoding.org. [Accessed 2017].

Vet Compass, “Vet Compass: Health Surveillance for UK companion animals,” 2017. [Online]. Available: http://www.rvc.ac.uk/VetCompass. [Accessed 2017].

von Holdt B. M., Pollinger J. P., Lohmueller K. E., Han E., Parker H. G., Quignon P., Degenhardt J. D., Boyko A. R., Earl D. A., Auton A., Reynolds A., Bryc K., Brisbin A., Knowles J. C., Mosher D. S., Spady T. C., Elkahloun A., Geffen E., Pilot M., Jedrzejewski W., Greco C., Randi E., Bannasch D., Wilton A., Shearman J., Musiani M., Cargill M., Jones P. G., Qian Z., Huang W., Ding Z., Zhang Y., Bustamante C. D., Ostrander E. A., Novembre J. and Wayne R. K., “Genome-wide SNP and haplotype analyses reveal a rich history underlying dog domestication,” Nature, vol. 464, pp. 898-903, 2010.

Yau P. P., Dhand N. K., Thomson P. C., and Taylor R. M., “Retrospective study on the occurrence of canine lymphoma and associated breed risks in a population of dogs in NSW (2001-2009),” Australian Veterinary Journal, vol. 95, no. 5, pp. 149-155, 2017.

Zandvliet M., “Canine lymphoma: a review,” Veterinary Quarterly, vol. 36, no. 2, pp. 76-104, 2016.