

ORIGINAL RESEARCH

Degree of osteophyte formation seen on radiographs provides useful prognostic information for dogs with cruciate ligament disease

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Abstract

Background: Concurrent osteoarthritis is generally present in the stifle joints of dogs with cranial cruciate ligament disease (CCLD), but it is not known if the degree of osteoarthritis-related changes affects the prognosis. Development of osteophytes is a key radiographic feature of osteoarthritis. The aim of this study was to evaluate the association between the degree of osteophyte formation seen on radiographs and CCLD-related euthanasia in dogs with CCLD.

Methods: A retrospective cohort study including 226 dogs treated for CCLD at two university animal hospitals was performed. Clinical and follow-up information was retrieved, and stifle radiographs taken during the 31 days before treatment for the CCLD were graded for osteophyte formation by three veterinary radiologists. A multivariable Cox proportional hazards model was applied to assess the association between the degree of osteophyte formation and CCLD-related euthanasia.

Results: An association between the degree of osteophyte formation and CCLD-related euthanasia was found, with increased osteophyte formation associated with an increased hazard of CCLD-related euthanasia (hazard ratio 1.06, 95% confidence interval 1.01–1.11, $p = 0.01$).

Limitations: No clinical assessment of the outcome was performed.

Conclusion: The findings suggest that evaluation of stifle radiographs for osteophyte formation could provide useful prognostic information for dogs with CCLD.

INTRODUCTION

Cranial cruciate ligament disease (CCLD) is one of the most common orthopaedic diseases in dogs, and the most common stifle joint disease requiring veterinary care.^{1,2} The disease is described as an 'organ failure' of the stifle joint, including synovitis and successive degeneration of the cranial cruciate ligament.³ Many factors, such as genetics, anatomical conformation and environment, are thought to contribute to disease development, although the exact aetiopathogenesis of the disease is unclear.^{3–7}

Osteoarthritis (OA) is generally present in the stifle at the time of CCLD diagnosis and progresses in the affected joint regardless of treatment method.^{8–10} OA involves degradation of the articular cartilage and

ligaments, and formation of osteophytes and is associated with a varying degree of inflammation, lameness and pain.^{11–13} Development of osteophytes is one of the key radiographic features of OA, and osteophytes progressively develop after experimental transection of the cranial cruciate ligament.¹⁴ The degree of OA-associated changes can be assessed by radiography, and many different grading systems have been reported.¹⁵ The degree of radiographically assessed OA in the stifle joint correlates with arthroscopic observations of synovitis severity in dogs with CCLD, even though arthroscopy is much more sensitive for detecting signs of synovitis.¹⁶

Chronic pain, such as pain due to OA, is linked to the quality of life of affected dogs.¹⁷ Severe cases may result in euthanasia if the owner perceives that

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the pain and impaired function has a great impact on their dog's life. In a previous study, we reported that 18.3% of dogs treated for CCLD were euthanased due to CCLD-related causes, of which the most common reason was persistent lameness of the affected hindlimb.¹⁸ The aim of the current study was to evaluate the association between the degree of stifle joint osteophyte formation before treatment initiation and CCLD-related euthanasia in dogs with CCLD. The hypothesis was that the degree of osteophyte formation and CCLD-related euthanasia are associated, and that the degree of osteophyte formation could serve as a potential prognostic indicator in future prospective studies of dogs with CCLD.

MATERIALS AND METHODS

Study design

A retrospective single cohort study of dogs treated for CCLD at two university animal hospitals (VHs, VH1: University Animal Hospital in Uppsala, Sweden, and VH2: University Animal Hospital in Oslo, Norway) between 1 January 2011 and 31 December 2016 was performed.

Data collection

Clinical data, including history, breed, age, body-weight, body condition score, sex (female/male, information about neuter status was unavailable in the medical records) and treatment method, were retrieved from the medical records. Follow-up information regarding the date and reason for euthanasia was obtained from the medical records and/or from standardised telephone interviews with the dog owners performed between 1 August and 15 October 2018. Referring veterinarians were contacted if needed (i.e., when the dog owner could not remember the date of euthanasia). Dates were recorded as the 1st of the month if the exact date was unknown.

Dogs with a CCLD diagnosis (confirmed by either a positive tibial compression test, a positive cranial drawer test or by inspection of the ruptured ligament during arthrotomy/arthroscopy) and radiographs of the affected stifle joint taken within 31 days before treatment initiation were included in the study. Exclusion criteria were dogs with only mild fraying of the cranial cruciate ligament (less than 10% rupture, assessed by visual inspection by the surgeon), prior contralateral CCLD, missing information about the duration of lameness before treatment initiation, less than 14 days follow-up time and/or radiographs of suboptimal image quality (assessed subjectively by the authors). In addition, dogs that were euthanased at the time of diagnosis or were less than 6 months old at treatment initiation were excluded.

Radiographic grading

Radiographs were independently graded by two board-certified veterinary radiologists (C. L. and J. I.) and a staff radiologist (V. N.) during 2019–2020. Anonymised images were assessed in random order using Digital Imaging and Communications in Medicine viewing software (Horos, www.horosproject.org). The osteophytes (including intra-articular and periarticular enthesophytes) were graded according to Wessely et al.,¹⁵ with the modification that a grading scale of 0–3 was used instead of the original grading scale of 1–4. Grade 0 represented normal joint margins/surfaces, grade 1 represented mild bone formation on joint margins, grade 2 represented moderate bone formation on joint margins and grade 3 represented severe formation on the joint margins. Fifteen stifle joint regions, considered to extend to the midpoint between adjacent regions, were evaluated. However, enthesiopathy in gastrocnemius insertion area was excluded from region number 10 since it is less likely to have a direct association with intra-articular OA joint changes.¹⁵ One assessment point (number 11) included three anatomical structures—the medial and lateral fabellae and the popliteal sesamoid bone—which were graded independently for osteophytes. Thus, 17 assessment points were included in the grading.

The lowest grade was chosen if the evaluator considered that a lesion was between two grades. After completion of the independent grading, the grades were compared between the three radiologists, and a final grade was decided by majority consensus. An osteophyte score was then generated for each dog, which consisted of the sum of the individual grades for all assessment points (range 0–51).

Outcome

CCLD-related euthanasia was classified as deaths where lameness or other clinical signs from the affected hindlimb, including subsequent CCLD of the contralateral limb, contributed to the decision of euthanasia (as described in Boge et al.¹⁸). The reasons for CCLD-related euthanasia were classified into five subcategories: persistent lameness, post-operative complications, subsequent contralateral CCLD, guarded prognosis for return to full function and other reasons. Deaths unrelated to CCLD were classified according to Fleming et al.,¹⁹ but with additional categories for 'behaviour-related' and 'high age'. In addition, death due to an unknown reason was recorded as 'unclassified'. Follow-up time was defined as the time from treatment initiation to owner contact/death/euthanasia, or to the last recorded visit in the medical record if the dog owner could not be reached.

Statistical analysis

All statistical analyses were performed in RStudio (version 4.0.0).²⁰ Categorical variables are presented as counts (percentage) and continuous variables as medians (min–max), since graphical assessment showed deviance from normality. Collinearity between the variables was tested by Spearman's rank-order correlation coefficient for continuous variables and by Goodman and Kruskal's gamma for categorical variables. Differences in osteophyte scores between the treatment groups and between dogs with unilateral CCLD and subsequent contralateral CCLD were evaluated with Kruskal–Wallis one-way analysis of variance, and pairwise comparisons between the treatment groups were then performed with the Wilcoxon signed-rank test. Kaplan–Meier survival curves were used to describe differences in survival times in the 25%, 50% and 75% of the dogs with the highest osteophyte scores compared with the rest of the dogs. Log-rank test was used to compare the survival curves.

A Cox proportional hazards model was used to evaluate the association between the osteophyte score and the hazard of CCLD-related euthanasia. Dogs that were classified as dead/euthanased for reasons unrelated to CCLD or alive at follow-up were censored in the analysis. Osteophyte score, as a continuous variable, was set as the main exposure variable. A causal diagram was created to identify potential confounders and intervening variables for the association between osteophyte score and CCLD-related euthanasia. All variables on the causal path from osteophyte score to the outcome were considered intervening variables, and thus not included in the statistical model.²¹ The following variables were considered for inclusion: age at diagnosis, bodyweight, breed (with separate categories for breeds represented by at least five dogs), duration of lameness before treatment initiation (subcategories: 0–2 weeks, 2–4 weeks, 4–6 weeks, 6–8 weeks and more than 8 weeks), overweight (assessed by the examining veterinarians and categorised as yes/no. 'Yes' included dogs with a body condition score of more than 5/9, more than 3/5 or that were subjectively judged as overweight. 'No' included dogs with a body condition score of 5/9 or less, 3/5 or less or that were subjectively judged as normal weight/underweight, as well as dogs with no information about body condition score/overweight in the medical record), concurrent non-orthopaedic comorbidities, concurrent orthopaedic comorbidities (subcategories: stifle joint osteochondrosis, hip dysplasia, patellar luxation and other orthopaedic comorbidities), sex, laterality of the affected limb and osteophyte score. The stifle with the highest osteophyte score was included in the statistical analysis for dogs that were presented with bilateral rupture. The only missing value was bodyweight in a female Gordon setter, and the average bodyweight from the breed standard was used for this dog (according to the Federation Cynologique Internationale). Univariable analyses were performed, and

all variables with p -values < 0.2 were considered for inclusion in the multivariable model, as well as interactions between these variables. The Wald test was used to evaluate the overall significance of multilevel categorical variables.

Manual stepwise backward elimination was used to select variables in the multivariable model, and p -values < 0.05 were considered to indicate statistical significance. Schoenfeld residuals were used to evaluate the assumption of proportional hazards, and sensitivity analysis was used to evaluate individual censoring. Plots of martingale residuals were used to check the functional form of the predictors, and deviance and scale score residuals were plotted against time at risk to detect outliers and influential observations. The model was refitted without the outlying and influential observations.

In addition, a Cox proportional hazards model was fitted with osteophyte score and treatment methods as the only predictors, to evaluate if the observed association between the osteophyte score and CCLD-related euthanasia was mediated through the intervening treatment method variable.

RESULTS

Animals

In total, 226 of the 436 dogs diagnosed with CCLD during the time period fulfilled the inclusion criteria, of which 124 (54.9%) were treated at VH1 and 102 (45.1%) at VH2. The median follow-up time was 2.8 years (15 days–7.5 years). The median age at CCLD diagnosis was 6.0 (0.6–12.5) years, and the median bodyweight was 29.0 (3.3–80.3) kg. The most common breeds were Rottweilers ($n = 22$, 9.7%), Golden retrievers ($n = 13$, 5.8%) and Labrador retrievers ($n = 10$, 4.4%), and 44 (19.5%) of the dogs were mixed breeds. Of the 226 dogs, 103 (45.6%) were males and 123 (54.4%) were females. In total, 59 (26.1%) dogs were classified as overweight or obese, and 102 (45.1%) dogs had been lame for more than 8 weeks at the time of diagnosis. Thirty-seven (16.4%) dogs were affected by concurrent non-orthopaedic disease, while 57 (25.2%) suffered concurrent orthopaedic disease, of which patellar luxation was the most common diagnosis ($n = 18$, 8.0%). The dogs were treated conservatively ($n = 36$, 15.9%) or surgically with either lateral fabellotibial suture (LFS, $n = 65$, 28.8%), tibial plateau levelling osteotomy (TPLO, $n = 62$, 27.4%), tibial tuberosity advancement (TTA, $n = 46$, 20.4%) or modified Maquet procedure (MMP, $n = 17$, 7.5%). Inspection of the intra-articular structures with either arthroscopy or arthrotomy was performed during the surgical CCLD procedure in 150 (66.4%) of the dogs, of which 38 (25.3%) were diagnosed with meniscal injuries. Four dogs (1.8%) presented with bilateral CCLD, and 69 dogs (30.8%) suffered subsequent CCLD during the follow-up period.

TABLE 1 The osteophyte score assessed on radiographs taken before treatment initiation in 226 dogs with cranial cruciate ligament disease treated at two university animal hospitals

Treatment	Osteophyte score
Conservative ($n = 36$)	8.5 (0–23)
Lateral fabellotibial suture ($n = 65$)	2 (0–17)
Tibial plateau levelling osteotomy ($n = 62$)	8 (0–29)
Tibial tuberosity advancement ($n = 46$)	6 (0–29)
Modified Maquet procedure ($n = 17$)	9 (0–15)
Total ($n = 226$)	6 (0–29)

Note: The scores are presented as median (min–max).

Grading of osteophytes

The median osteophyte score was 6 (0–29, see Figure S1 for the distribution), and varied with treatment (see Table 1). Group-wise comparisons with the Wilcoxon signed-rank test revealed that the dogs treated by LFS had significantly lower osteophyte scores before treatment initiation compared with dogs treated with the other methods. There was no significant difference between the osteophyte score of the index stifle in dogs that were affected by subsequent contralateral CCLD and that of dogs that were unilaterally affected ($p = 0.498$). The osteophyte score was not significantly different between dogs classified as overweight and those that were not (median scores 5 and 6, respectively, $p = 0.772$).

Outcome

In total, 43 (19.0%) of the dogs were euthanased because of CCLD-related causes. Concurrent comorbidities contributed to the decision about euthanasia in 11 dogs (25.6%). In the 11 dogs with CCLD-related problems and comorbidities, there were nine dogs where the CCLD-related problems and not the comorbidity were the main reason for euthanasia and two

dogs where the comorbidities were the main reasons for the euthanasia. For more information about the comorbidities, please see Table S1. The dogs that were euthanased due to CCLD had higher osteophyte scores than dogs that were still alive or were euthanased for reasons other than CCLD (median score 9 [0–29] compared to 5 [0–29], $p = 0.009$). The median time from treatment initiation to CCLD-related euthanasia was 1.1 years (15 days–6.2 years). The most common reasons for CCLD-related euthanasia were persistent lameness (16 dogs, 7.1%), subsequent rupture of the contralateral cruciate ligament, often in combination with unsuccessful recovery after the initial CCLD (14 dogs, 6.2%), and postoperative complications (seven dogs, 3.1%). Of the postoperative complications that resulted in euthanasia, four (57.1%) were surgical site infections and three (42.9%) were implant failures. Seventy-six (33.6%) dogs were euthanased or died due to causes other than CCLD, and 107 (47.3%) dogs were alive at follow-up. The median time to censoring was 3.0 years (18 days–7.5 years).

Survival analysis

Kaplan–Meier survival curves comparing survival in the 25%, 50% and 75% of dogs with highest osteophyte scores with the rest of the dogs are presented in Figure 1. Osteophyte scores of 11, 6 and 2 were used as cut-offs, but since several dogs had the same osteophyte score, the final groups included 26.5% (60 dogs), 50.4% (114 dogs) and 77.9% (176 dogs). The log-rank test showed a significant difference between the survival curves when 11 and 6 were used as the cut-offs ($p = 0.0096$ and 0.023 , respectively).

The results from the univariable Cox proportional hazards models are presented in Table 2, and those from the final multivariable Cox proportional hazards model are presented in Table 3. The final model included osteophyte score as the only predictor

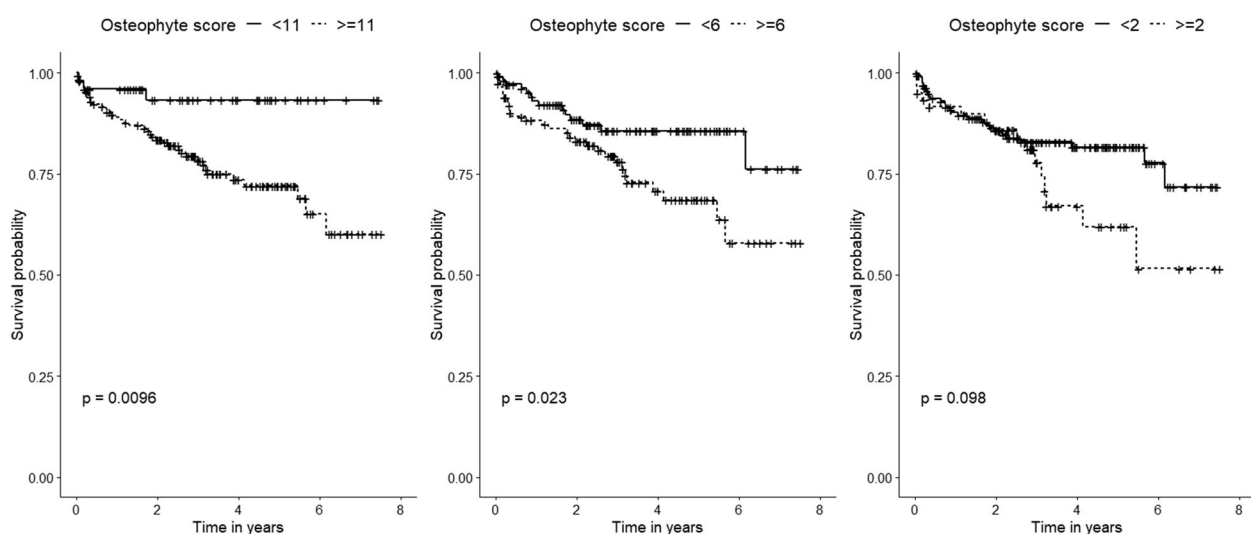


FIGURE 1 Kaplan–Meier survival curves for dogs with osteophyte scores ≥ 11 and < 11 , ≥ 6 and < 6 , and ≥ 2 and < 2 in a cohort of dogs with cranial cruciate ligament disease

TABLE 2 Univariable Cox proportional hazards models for selection of variables to assess the association between the degree of osteophyte formation before treatment initiation and cranial cruciate ligament disease (CCLD)-related euthanasia in 226 dogs with CCLD

Variable	<i>p</i> -Value
Age (years) ^a	0.164
Bodyweight (kg) ^a	0.229
Breed	0.583 ^b
Lameness duration ^a	0.347 ^b
Laterality of limb	0.818
Non-orthopaedic comorbidity ^a	0.998
Orthopaedic comorbidity ^a	0.331 ^b
Osteophyte score ^c	0.014
Overweight ^a	0.279
Sex	0.945

^aAt time of diagnosis.

^b*p*-Values from Wald test are presented for multilevel categorical variables.

^cBefore treatment initiation.

TABLE 3 Results from a multivariable Cox proportional hazards model assessing the association between the degree of osteophyte formation before treatment initiation and cranial cruciate ligament disease (CCLD)-related euthanasia in 226 dogs with CCLD

Variable	Hazard ratio	95% confidence interval	<i>p</i> -Value
Osteophyte score	1.06	1.01–1.11	0.014

(hazard ratio 1.06, $p = 0.01$), all other variables were excluded during the model building process. A few influential and outlying observations were detected, and the model was refitted without these observations without substantial changes.

Treatment was not significant ($p = 0.061$) in the alternative model where the treatment variable was included, while the osteophyte score variable was still significant ($p = 0.022$).

DISCUSSION

In this study, an association between the degree of radiographically assessed osteophyte formation before treatment initiation and CCLD-related euthanasia in dogs with CCLD was found, with the hazard of CCLD-related euthanasia increasing by 6% for every increase in osteophyte score. Methods that give prognostic information are highly valuable when decisions regarding treatment are made, and this suggests a worse prognosis in dogs with higher osteophyte scores. However, the causality needs to be confirmed in future, prospective studies.

Dogs with CCLD generally develop progressive OA, which has a substantial impact on the welfare of the affected dogs.^{9,14,22–24} The relationship between radiographic evidence of stifle joint OA and pain/function in dogs has been evaluated in several studies, but there are still knowledge gaps and there is no consensus regarding the best method for pain evaluation in

dogs with OA.^{10,25,26} Gordon et al.²⁶ assessed the relationship between limb function and radiographically assessed stifle joint OA in dogs by evaluation of ground reaction forces, and they concluded that the presence of OA did not correlate with clinical function. However, Ashour et al.¹⁰ found that the severity of radiographically assessed OA at diagnosis of CCLD correlated with pain on internal stifle rotation during clinical examination, and Felson et al.²⁷ reported a correlation between the grade of osteophytes and the occurrence of pain in human stifle joints. Brown et al.²⁸ evaluated improvement in pain scores, as assessed by owners using the Canine Brief Pain Inventory questionnaire, and lameness, assessed by force plate gait analysis, in dogs with OA before and after treatment with NSAIDs. There was no correlation between the scores on the questionnaire and the results from the force plate gait analysis, even though both outcome measures showed improvement. The authors concluded that the owners were more focused on behaviours, such as the dog's ability to perform activities in the daily life in the home environment, than lameness. Thus, evaluation of function and pain in dogs with OA by force plate gait analysis in a clinic situation might be insufficient for assessment of the full impact of OA on the affected dog's function, severity of pain and quality of life. This could explain the results of the current study; the owners might have perceived that dogs with high osteophyte scores had an impaired quality of life and that the disease had a large impact on the dogs' everyday life, which resulted in a decision of euthanasia.

Another possible explanation for the association between osteophyte score and CCLD-related euthanasia is that the degree of osteophyte formation affected the examining veterinarians' recommendations for further treatment in dogs that did not recover according to plan. It might be that the veterinarians were more prone to recommend euthanasia if treatment failure occurred and the dog had extensive osteophyte formation.

Subsequent contralateral CCLD was common in the study population (69 dogs, 30.8%), and several dogs (14 dogs, 6.2%) were euthanased at the time of the subsequent cranial cruciate ligament rupture. These dogs were classified as euthanased because of CCLD-related causes. It could be argued whether this classification was correct, as the index stifle was not the main reason for euthanasia. However, nearly all dog owners stated that the dog had not fully recovered from the CCLD of the index stifle, or that the recovery period had been tough after the first CCLD treatment, and they did not want their dog to go through that again. Thus, it was often a combination of unsuccessful recovery from the first CCLD and the subsequent contralateral CCLD that resulted in a decision of euthanasia.

Survival analysis was used to evaluate the association between the osteophyte score and CCLD-related euthanasia. One of the major advantages of time to event analysis is that dogs can contribute with information as long as they are observed. Selection bias can be introduced in studies that evaluate the

impact of OA on clinical function if dogs that are euthanased due to severe OA are excluded from the follow-up evaluation. However, it is important to consider that survival only represents one measure of treatment outcome, and no clinical assessment was included in the current study.

Some further limitations should be mentioned. The categorisation of euthanasia as CCLD-related or not relied on the authors' retrospective judgement and was based on the information in the medical records and/or the interviews with the dog owners. A decision of euthanasia is often complex, and there is a risk that misclassification bias was introduced. However, any introduced bias was likely non-differential. Some dogs had comorbidities that contributed to the decision of euthanasia, and it can be argued whether these deaths should have been classified as CCLD-related or not. For consistency, all cases where the owner or veterinarian stated that CCLD was the main or contributing reason for euthanasia were classified as CCLD-related, regardless of the type and severity of the comorbidity. The exact importance of the comorbidity versus the importance of CCLD on the decision of euthanasia could not be evaluated in this retrospective setting.

The variable for overweight was based on the information available in the medical records, and dogs were classified as normal weight/underweight if there was no comment regarding overweight or increased body condition score in the medical record. Thus, there is a risk of misclassification bias due to underreporting of overweight dogs.

The dogs were not routinely radiographically screened for other orthopaedic comorbidities, and thus there is a risk that some orthopaedic comorbidities were missed. However, orthopaedic comorbidities resulting in clinical signs and hip/elbow dysplasia diagnosed via the official screening programme were registered, based on the information in the medical record. Although some cases of orthopaedic comorbidities might have been missed, the most important comorbidities (i.e., the ones resulting in clinical signs) were probably registered and included in the analysis.

Only dogs with radiographs of the affected stifle joint taken within 31 days before treatment initiation were included in the study. This inclusion criterion might have induced selection bias if the decision to take radiographs was influenced by the treatment method (i.e., if dogs treated with osteotomy procedures [TPLO, TTA, MMP] were radiographed to a greater extent than dogs treated conservatively or with LFS). Furthermore, treatment was not randomly assigned due to the retrospective nature of this study. To assess if the association between osteophyte score and CCLD-related euthanasia could instead have been an association between treatment method and CCLD-related euthanasia, as the osteophyte score varied with treatment, a separate model including treatment was conducted. The treatment variable did not reach statistical significance ($p = 0.061$), while the osteophyte variable did ($p = 0.022$). Therefore, we consider it unlikely that the association between osteophyte score and CCLD-related euthanasia was significantly influenced by treatment method. However, it cannot

be excluded that some of the observed association was related to differences between treatment methods. Prospective studies are needed to explore whether the association between osteophyte score and CCLD-related euthanasia is influenced by treatment method.

There is a risk that the presence of meniscal injury confounded the association between osteophyte score and CCLD-related euthanasia, if dogs with meniscal injuries had higher osteophyte scores, as has been reported previously.¹⁰ However, this could not be evaluated as arthrotomy/arthroscopy was not performed in all dogs. Furthermore, the study included dogs treated at referral veterinary hospitals, which might limit the generalisability of the results. Finally, some anatomical regions could be included in two grading areas, and changes in that region could therefore score double points, which may have influenced the overall osteophyte score.

CONCLUSION

An association between the degree of osteophyte formation assessed on radiographs taken before treatment initiation in dogs with CCLD and CCLD-related euthanasia was found, with increased osteophyte formation in the stifle joint being associated with an increased hazard of CCLD-related euthanasia. This finding suggests that evaluation of stifle radiographs for osteophyte formation can provide useful prognostic information for dogs with CCLD. Prospective studies are needed to confirm this association and further investigate any possible association with treatment methods.

AUTHOR CONTRIBUTIONS

Gudrun Seeberg Boge, Karolina Engdahl and Charles Ley planned the study, with input from Veronica Näslund and Jessica Ingman. Gudrun Seeberg Boge and Karolina Engdahl collected the data. Charles Ley, Veronica Näslund and Jessica Ingman assessed the radiographs and modified the model for osteophyte grading. Karolina Engdahl performed the data analysis and wrote the manuscript, with substantial input from all co-authors. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.


ETHICS STATEMENT

According to Swedish regulations, ethical approval is not necessary for a retrospective study such as this.


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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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