The Veterinary Journal 292 (2023) 105952

Contents lists available at ScienceDirect

The Veterinary Journal

journal homepage: www.elsevier.com/locate/tvjl

Risk factors for unilateral cranial cruciate ligament rupture diagnosis and for clinical management in dogs under primary veterinary care in the UK

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ARTICLE INFO

Keywords:
Cranial cruciate ligament
Dog
Electronic medical record
Primary-care
VetCompass

ABSTRACT

This study aimed to evaluate demographic risk factors associated with unilateral cranial cruciate ligament (CCL) rupture diagnosis and to explore demographic and clinical risk factors associated with management of unilateral CCL rupture in dogs under primary veterinary care in the UK. A retrospective cohort study design was used. Clinical records were automatically searched and manually verified for incident cases of unilateral CCL rupture during 2019 and additional clinical management information extracted. Multivariable logistic regression modelling was used to evaluate associations between risk factors and: (1) CCL rupture diagnosis; and (2) clinical management (surgical or non-surgical). The analysis included 1000 unilateral CCL rupture cases and a random selection of 500,000 non-cases. After accounting for confounding factors, dogs aged 6 to < 9 years, male neutered and female neutered dogs, insured dogs, and Rottweiler, Bichon Frise, and West Highland White terrier breeds, in particular, had increased odds of unilateral CCL rupture diagnosis. Insured dogs and dogs ≥ 20 kg had increased odds of surgical management, while dogs ≥ 9 years and dogs with one non-orthopaedic comorbidity at diagnosis with CCL rupture had reduced odds. These findings inform identification of at-risk dogs, with Rottweilers and Bichon Frise particularly predisposed. Additionally, they contribute to a greater understanding of the clinical rationales used in primary-care veterinary practices to decide between surgical or non-surgical management of unilateral CCL rupture.

Introduction

Cranial cruciate ligament (CCL) rupture is one of the most frequent specific causes of lameness in dogs (Johnson et al., 1994), with prevalence estimates ranging from 0.56% to 2.55%, depending on the data source (Witsberger et al., 2008; Adams et al., 2011; Taylor-Brown et al., 2015; Engdahl et al., 2021; O'Neill et al., 2021a). CCL rupture is, in the majority of cases, characterised by a gradual degeneration of the extracellular matrix of the ligament leading to rupture (Comerford et al., 2011), although acute traumatic rupture of the CCL is also possible (Taylor-Brown et al., 2015). The underlying pathophysiology of the extracellular matrix degeneration remains unclear, but is considered complex and multifactorial (Hayashi et al., 2004). It is reported that 4–10% of dogs with CCL rupture initially present clinically with bilateral rupture (Buote et al., 2009; Grierson et al., 2011; Muir, 2018), while in dogs initially presenting with unilateral rupture, the contralateral stifle is affected within a year in up to 40% of cases (Doverspike et al., 1993).

Reported risk factors for diagnosis of CCL rupture include breed, sex, neuter-status, age, and bodyweight (Whitehair et al., 1993; Duval et al., 1999; Witsberger et al., 2008; Adams et al., 2011; Guthrie et al., 2012). A study based on UK veterinary primary-care data identified Rottweilers, West Highland White terriers, Golden retrievers, Yorkshire terriers and Staffordshire bull terriers at increased risk of CCL disease compared with crossbred dogs, while Cocker spaniels had reduced risk (Taylor-Brown et al., 2015). A more recent study using insurance data in Sweden identified 26 breeds at increased risk of CCL rupture compared to dogs not of that breed, including the Boerboel, Perro de Presa Canario, American and English bulldog, Dogue de Bordeaux, Bullmastiff, Chow Chow, Rottweiler, and Cane Corso, while 18 breeds had reduced risk including the Cocker spaniel, German shepherd dog, Chihuahua,

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https://doi.org/10.1016/j.tvjl.2023.105952
Received 11 November 2022; Received in revised form 17 January 2023; Accepted 23 January 2023
Available online 25 January 2023
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Miniature schnauzer, Shih-Tzu, English Springer spaniel, Pug, and Standard Dachshund (Engdahl et al., 2021). While some breeds (e.g. Rottweiler and Cocker spaniel) had consistent directions of predisposition or protection across both studies, others were only evident in one or other, which could indicate true risk differences but may simply reflect study limitations such as underpowering. Previous studies have identified bitches at greater risk than male dogs, and neutered dogs at greater risk than entire dogs (Slauterbeck et al., 2004; Witsberger et al., 2008; Buote et al., 2009; Taylor-Brown et al., 2015). Higher absolute bodyweight and relative within-breed bodyweight have both been associated with increased risk of CCL rupture (Whitehair et al., 1993; Taylor-Brown et al., 2015). Median age at first diagnosis of CCL rupture is reported from 4.3 to 7.1 years (Guthrie et al., 2012; Taylor-Brown et al., 2015; Engdahl et al., 2021). One study reported that lower age at diagnosis was more common in large and giant breeds than in small breeds (Engdahl et al., 2021).

A major clinical decision for management of CCL rupture is between surgical and non-surgical management (Kirkness, 2020). Although surgical management remains the published reference standard treatment for CCL rupture (Kirkness, 2020), there is some evidence that dogs weighing 15 kg or less can be successfully managed non-surgically. A US-based study on dogs presenting to a referral veterinary medical teaching hospital for CCL rupture reported that, among dogs managed non-surgically, 86% of dogs weighing $\leq$ 15 kg were considered clinically normal or improved after an average follow-up of 3 years, compared with 19% of dogs weighing $>$ 15 kg managed non-surgically (Vasseur, 1984). A more historic UK-based study reported that 90% of small-breed dogs managed non-surgically had no detectable lameness reported by the owner versus 78% of large-breed dogs; but time to recovery was not clear from the publication (Pond and Campbell, 1972). However, inference from both these studies was limited by their relatively small sample sizes of 85 and 107 affected dogs respectively, and by their descriptive study design whereby neither study compared non-surgical to surgical management.

A pervading veterinary view that larger dogs have increasing requirement for surgery is reflected in a UK primary-care study where the probability of undergoing surgery increased as bodyweight increased, from 56% in dogs weighing $<$ 10 kg to 86% in dogs weighing $\geq$ 40 kg (Taylor-Brown et al., 2015). A survey-based study suggested an even lower probability of surgery in small dogs, with only 15.5% of UK veterinarians supporting a recommendation for immediate surgical management of CCL rupture in dogs weighing under 15 kg (Comerford et al., 2013). Although bodyweight may affect the chosen management, decision-making between surgical and non-surgical management is likely multifactorial, with severity of lameness, degree of stifle instability, owner preference, age, comorbidities, and financial restrictions also possibly important (Comerford et al., 2013; Kirkness, 2020). However, to date, the factors affecting clinical management of CCL rupture have not been epidemiologically analysed.

Using anonymised veterinary clinical data, this study aimed to identify demographic risk factors associated with CCL rupture diagnosis in dogs. The study also aimed to explore demographic and clinical risk factors associated with clinical management decision-making of CCL rupture. Based on previous evidence (Comerford et al., 2013; Taylor-Brown et al., 2015), the study hypothesized that increasing bodyweight is associated with increasing odds of surgical management relative to non-surgical management in dogs with CCL rupture. Given a prevailing veterinary view that surgical management offers the reference standard for CCL rupture (Kirkness, 2020), this study aimed to deconstruct the clinical factors used in primary-care veterinary practices to decide between surgical or non-surgical management.

Materials and methods

Study design and power calculation

VetCompass collates de-identified electronic medical record (EMR) data from primary-care veterinary practices in the UK for epidemiological research (VetCompass, 2019). The study population included all available dogs under primary veterinary care at clinics participating in the VetCompass Programme during 2019. Dogs under veterinary care were defined as those with at least one electronic medical record (EMR; free-text clinical note, treatment, or bodyweight) recorded during 2019. Available data fields included a unique animal identifier along with species, breed, date of birth, sex, neuter status, insurance status, and bodyweight, and clinical information from free-form text clinical notes, summary diagnosis terms (The VeNom Coding Group, 2019), and treatment with relevant dates.

The study used a retrospective cohort design. Sample size calculations in Epi info (CDC) estimated that approximately 396 dogs managed surgically for CCL rupture and 131 dogs managed non-surgically would be required to identify if dogs $\geq$ 10 kg had at least twice the odds of surgical management (relative to non-surgical management) compared to dogs $<$ 10 kg, assuming 70% of dogs $\geq$ 10 kg are managed surgically, a 3:1 ratio of dogs $\geq$ 10 kg to $<$ 10 kg (Pegram et al., 2021a), 90% power, and 95% confidence (Epi Info 7 CDC, 2019).

Ethics approval was obtained from the RVC Social Sciences Ethical Review Board (Reference number, SR2018–1652; Approval date, 2 October 2018).

Case identification and definition

The case definition required a final diagnosis of unilateral CCL rupture recorded in the EMR. Exclusion criteria included: (a) prior CCL rupture or stifle pathology; and (b) bilateral CCL rupture at diagnosis.

Incident, rather than prevalent, cases were included in the study, with these cases defined as dogs that were first diagnosed with CCL rupture between January 1 and December 31 of 2019. Candidate cases were identified by applying search terms relevant to the diagnosis and management of CCL rupture in the clinical notes during 2019 (acl, ccl, cranial draw*, cruciate rupture~1, cruciate ligament~1, tta, tplo, lateral sut*, extracapsular sut*). The search findings were merged, and a subset of candidate cases (n = 3601/32654; 11.0%), randomly presented through the online database using the RAND function in SQL Server (Microsoft Learn, 2019), had their clinical notes examined manually in detail to identify whether they met the case definition i.e. excluding dogs with bilateral CCL rupture at diagnosis and prior stifle pathology. The remaining non-candidate dogs were classified as non-cases, with 500,000 non-cases randomly selected using the RAND function in SQL Server (Microsoft Learn, 2019) as controls. Demographic data for cases and non-cases were extracted automatically from the VetCompass database. Data relating to clinical management of cases were extracted manually from their EMR.

Data preparation

Data were prepared separately for: (a) the disorder risk analysis (with CCL rupture or non-CCL rupture as the outcome of interest); and (b) the clinical management analysis (with surgical or non-surgical management of CCL rupture as the outcome of interest). Breed information entered by the participating practices was cleaned and mapped to a VetCompass breed list derived and extended from the VeNom Coding breed list (The VeNom Coding Group, 2019). To maintain sufficient power for analysis, the breed variable included all individual breeds with at least 15 cases of CCL rupture or over 10,000 non-cases in the overall disorder risk analysis. For the clinical management analysis, the breed variable included all specific breeds with at least five dogs managed surgically or five dogs managed non-surgically. For both

analytic datasets, the remaining dogs were grouped as either 'Purebred – other' or 'Crossbred'. Neuter status was defined by the final available EMR neuter value and was combined with sex to create four categories: female entire, female neutered, male entire, and male neutered.

Adult bodyweight was defined as the median of all bodyweight (kg) values recorded for each dog after reaching 18 months old and was categorised as: < 10, 10 to < 20, 20 to < 30 and ≥ 30. For the disorder risk analysis, the median adult bodyweight was calculated for each sex of every purebred breed with at least 100 dogs in the overall study population; this variable was called 'breed-sex median'. For each purebred dog in the current sample, adult bodyweight was categorised as 'at or above the breed-sex median,' and 'below the breed-sex median'; this variable was called 'bodyweight relative to breed-sex median'. The age (years) of cases was calculated at the date of first diagnosis of CCL rupture. The age of non-cases was defined as the age (years) on December 31, 2019. Age (years) was categorised: < 3, 3 to < 6, 6 to < 9, 9 to < 12, and ≥ 12. Veterinary group attended was categorised as 1–6, based on the six practice groups involved in the study. Insurance status was categorised as insured or uninsured at the final EMR.

For CCL rupture cases only, additional data were collected on: clinical management (with management defined as surgical – including any technique for stabilisation of the stifle joint – or non-surgical management assigned at diagnosis), body condition status (at CCL rupture diagnosis or within 12 months prior; defined as 'overweight/obese', 'ideal bodyweight' or 'underweight', according to information recorded within the EMR (Pegram et al., 2021b)), orthopaedic comorbidities at CCL rupture diagnosis (defined as a disorder diagnosis by a veterinary surgeon at or within one month prior to date of CCL rupture diagnosis and was included as a distinct disorder in logistic regression modelling if at least 10 dogs managed either surgically or non-surgically were affected, otherwise recorded as 'other comorbid disorders'), and number of non-orthopaedic comorbidities at CCL rupture diagnosis (defined as a disorder diagnosis by a veterinary surgeon at or within one month prior to date of CCL rupture diagnosis and categorised as '0', '1', or '≥2' for logistic regression modelling. Categories were combined to ensure five or more dogs in one group.

Where information for a study variable was not documented in the EMR, the status was recorded as 'Not recorded' and included as a separate category in the analysis if the 'Not recorded' category accounted for >10% of the study variable (Pegram et al., 2021b).

Statistical analysis

Following data checking for internal validity and cleaning in Excel (Microsoft Office Excel 2013, Microsoft Corp.), analyses were conducted using R version 4.0.2 (R Core Team). Continuous variables were assessed graphically for their distribution and summarised using median, interquartile range (IQR), and range if non-normally distributed. Chi-square or Fisher's exact test was used to compare categorical variables and the Student's t-test or Mann-Whitney U test to compare continuous variables as appropriate (Kirkwood and Sterne, 2003).

Logistic regression modelling was used to evaluate univariable associations between: (1) risk factors (breed, adult bodyweight, bodyweight relative to breed-sex median, age, sex-neuter status, veterinary group, and insurance status) and CCL rupture diagnosis; and (2) risk factors (breed, adult bodyweight, age, sex-neuter status, insurance status, body condition status, orthopaedic comorbidities at diagnosis, and number of non-orthopaedic comorbidities at diagnosis) and surgical management (in dogs with unilateral CCL rupture diagnosis only).

Risk factors with liberal associations in univariable modelling ($P < 0.2$) were taken forward for multivariable evaluation. Model development used manual backwards stepwise elimination. All eliminated factors were re-evaluated for confounding effects within the provisional-final model using the change-in-estimate approach such that a change in the odds ratio for a primary exposure variable of more than 10% was considered to represent important confounding (Dohoo et al., 2009). If both breed and adult bodyweight were significant at the univariable stage, adult bodyweight (a defining characteristic of and highly correlated with breed) was excluded from the initial breed multivariable modelling. Instead, this variable individually replaced the breed variable in the main final model to evaluate its effects after taking account of the other variables (O'Neill et al., 2018). Biologically relevant pairwise interactions between final model variables were assessed using the likelihood ratio test with a cut-off of $P < 0.05$ (EFSA Scientific Committee, 2011). Veterinary group attended was evaluated as a fixed effect to adjust for clustering at the clinic level. The area under the ROC curve and the Hosmer-Lemeshow test were used to evaluate the quality of the model fit (Dohoo et al., 2009). Statistical significance was set at the 5% level. Figures were created in R statistical software (R version 4.0.2) using the 'forestplot' package (Gordon and Lumley, 2017).

Results

Descriptive analysis for CCL cases and non-cases

Descriptive analysis included 1000 unilateral CCL rupture cases and 500,000 non-cases (Table 1). The median age of cases (7.4 years; IQR, 5.1–9.5 years; range, 0.5–16.2 years) was older than the median age of non-cases (5.3 years; IQR, 2.3–9.0 years; range, 0.0–25.0 years; $P < 0.001$). The median adult bodyweight of cases (13.3 kg; IQR, 7.7–26.2 kg; range, 1.0–65.1 kg) did not significantly differ to the median adult bodyweight of non-cases (13.7 kg; IQR, 8.4–24.4 kg; range, 1.5–106.0 kg; $P = 0.327$). The most common breeds among cases were the Jack Russell terrier (6.9%; n = 69), Labrador retriever (6.2%; n = 62), Staffordshire bull terrier (4.1%; n = 41), and West Highland White terrier (3.9%; n = 39), along with 28.2% (n = 282) crossbreds. The most common breeds among non-cases were the Labrador retriever (6.9%; n = 34,429), Jack Russell terrier (4.5%; n = 22,540), Cocker spaniel (4.4%; n = 21,847), and Staffordshire bull terrier (4.2%; n = 20,897), along with 23.8% (n = 119,044) crossbreds (Table 1).

Disorder risk analysis

All tested variables were liberally ($P < 0.2$) associated with unilateral CCL rupture diagnosis in univariable logistic regression modelling. Following evaluation using multivariable logistic regression, the final breed-based model comprised five risk factors: breed, age, sex-neuter status, insurance status, and veterinary group (Fig. 1). No biologically relevant interactions were identified. After accounting for the effects of the other variables evaluated, six breeds had increased odds of CCL rupture compared with crossbred dogs. The breeds with the highest odds were the Rottweiler (OR, 3.66; 95% CI, 2.34–5.73; $P < 0.001$), Bichon Frise (OR, 2.09; 95% CI, 1.43–3.05; $P < 0.001$), West Highland White terrier (OR, 1.80; 95% CI, 1.28–2.53; $P < 0.001$), Golden retriever (OR, 1.69; 95% CI, 1.13–2.51; $P = 0.010$), Yorkshire terrier (OR, 1.53; 95% CI, 1.09–2.15; $P = 0.015$), and Jack Russell terrier (OR, 1.43; 95% CI, 1.10–1.87; $P = 0.008$). Eight breeds had reduced odds of CCL rupture compared with crossbreds including: Cockapoo (OR, 0.26; 95% CI, 0.14–0.51, $P < 0.001$), Chihuahua (OR, 0.31; 95% CI, 0.14–0.65; $P = 0.002$), Shih-Tzu (OR, 0.41; 95% CI, 0.24–0.71; $P = 0.001$), and German shepherd dog (OR, 0.43; 95% CI, 0.23–0.81; $P = 0.009$). Dogs aged 6 to < 9 years had the highest odds of CCL rupture (OR, 3.24; 95% CI, 2.58–4.07, $P < 0.001$) compared with dogs < 3 years. Neutered females (OR, 1.46; 95% C, 1.19–1.79, $P < 0.001$) and neutered males (OR, 1.42; 95% CI, 1.16–1.74; $P < 0.001$) had increased odds compared with entire females. The risk in male entire dogs (OR, 0.86; 95% CI, 0.69–1.08; $P = 0.195$) did not significantly differ to the risk in female entire dogs. Insured dogs had 6.25 (95% CI, 5.45–7.16; $P < 0.001$) times the odds of CCL rupture compared with uninsured dogs (Fig. 1). The Hosmer-Lemeshow test indicated no evidence of poor model fit ($P = 0.300$) and the area under ROC curve (0.793) indicated good ability to differentiate cases and non-cases.

Table 1
Relative unilateral cranial cruciate ligament rupture case count (% of total cases; n = 1000) and non-case count (% of total non-cases; n = 500,000) for categorical variables recorded in dogs attending primary-care veterinary practices in the UK.

Variable	Category	Cases (% total)	Non-cases (% total)
Breed	Crossbreed	282 (28.2)	119,044 (23.8)
	Purebreed - other	220 (22.0)	143,783 (28.9)
	Jack Russell terrier	69 (6.9)	22,540 (4.5)
	Labrador retriever	62 (6.2)	34,429 (6.9)
	Staffordshire bull terrier	41 (4.1)	20,897 (4.2)
	West Highland White terrier	39 (3.9)	7902 (1.6)
	Yorkshire terrier	38 (3.8)	11,810 (2.4)
	Cocker spaniel	36 (3.6)	21,847 (4.4)
	English springer spaniel	34 (3.4)	9009 (1.8)
	Bichon Frise	30 (3.0)	5439 (1.1)
	Golden retriever	27 (2.7)	6111 (1.2)
	Rottweiler	21 (2.1)	2892 (0.6)
	Border terrier	19 (1.9)	5494 (1.1)
	Border collie	16 (1.6)	12,894 (2.6)
	Beagle	15 (1.5)	4541 (0.9)
	Shih-tzu	14 (1.4)	15,193 (3.1)
	French bulldog	10 (1.0)	14,785 (3.0)
	German shepherd dog	10 (1.0)	10,605 (2.1)
	Cockapoo	9 (0.9)	16,180 (3.2)
	Chihuahua	7 (0.7)	12,704 (2.6)
Age (years)	< 3	109 (10.9)	156,151 (31.2)
	3 to < 6	209 (20.9)	119,390 (23.9)
	6 to < 9	383 (38.3)	96,581 (19.3)
	9 to < 12	230 (23.0)	72,191 (14.4)
	≥ 12	66 (6.6)	51,702 (10.3)
	Not recorded	3 (0.3)	3985 (0.8)
Bodyweight (kg)	< 10	348 (34.8)	120,604 (24.1)
	10 to < 20	208 (20.8)	106,812 (21.4)
	20 to < 30	157 (15.7)	67,341 (13.5)
	≥ 30	154 (15.4)	50,960 (10.2)
	Not recorded	133 (13.3)	154,283 (30.9)
Bodyweight relative to breed-sex median	At or above	331 (33.1)	130,795 (26.2)
	Below	278 (27.8)	129,657 (25.9)
	Not recorded	391 (39.1)	239,548 (47.9)
Sex-neuter status	Female entire	155 (15.5)	131,383 (26.3)
	Female neutered	335 (33.5)	106,059 (21.2)
	Male entire	165 (16.5)	147,596 (29.5)
	Male neutered	344 (34.4)	110,757 (22.2)
	Not recorded	1 (0.1)	4205 (0.8)
Insurance status	Uninsured	384 (38.4)	400,857 (80.2)
	Insured	616 (61.6)	99,143 (19.8)
Veterinary Group	1	279 (27.9)	173,753 (34.8)
	2	1 (0.1)	502 (0.1)
	3	316 (31.6)	131,711 (26.3)
	4	26 (2.6)	7127 (1.4)
	5	182 (18.2)	85,999 (17.2)
	6	196 (19.6)	100,908 (20.2)

Adult bodyweight was a significant risk factor when used to replace the breed variable in the final bodyweight-based model (Fig. 2). Dogs weighing 10 to < 20 kg (OR, 0.61; 95% CI, 0.51–0.72; P < 0.001) and dogs weighing 20 to < 30 kg (OR, 0.71; 95% CI, 0.58–0.85; P < 0.001) had reduced odds of CCL rupture when compared with dogs < 10 kg.

Descriptive analysis for surgical and non-surgical CCL cases

Among the 1000 cases of CCL rupture, 684 (68.4%) were managed surgically and 239 (23.9%) managed non-surgically. Management was not recorded in 77 (7.7%) dogs, which were excluded from further analysis. The median age of surgical cases (7.0 years; IQR, 4.9–8.8 years; range, 0.5–16.2 years) was younger than the median age of non-surgical cases (8.8 years; IQR, 6.3–11.0 years; range, 0.5–15.5 years; P < 0.001). The median adult bodyweight of surgical cases (17.7 kg; IQR, 10.0–29.0 kg; range, 2.6–62.2 kg) was heavier than the median adult bodyweight of non-surgical cases (11.4 kg; IQR, 7.8–21.7 kg; range, 2.6–65.1 kg; P < 0.001). The most common breeds among surgical cases were the Labrador retriever (7.0% of surgical cases; n = 48), Jack Russell terrier (6.0%; n = 41), Staffordshire bull terrier (4.4%; n = 30), and West Highland White terrier (3.8%; n = 26), in addition to 191 (27.9%) crossbreds. The most common breeds among non-surgical cases were the Jack Russell terrier (10.0%; n = 24), West Highland White terrier (5.4%; n = 13), Cocker spaniel (5.0%; n = 12), and Yorkshire terrier (5.0%; n = 12), in addition to 65 (27.2%) crossbreds (Table 2).

Clinical management analysis

All tested variables, except for sex-neuter status, were liberally (P < 0.2) associated with management of CCL rupture in univariable logistic regression modelling. Following evaluation using multivariable logistic regression, the final model comprised four risk factors: age, adult bodyweight (with breed not a significant risk factor when replacing bodyweight), insurance status, and number of non-orthopaedic comorbidities at diagnosis (Fig. 3). No biologically significant interactions were identified, therefore only main terms (rather than interaction terms) were included in the modelling. After accounting for the effects of the other variables evaluated, dogs aged 9 to < 12 years (OR, 0.53; 95% CI, 0.28–0.97; P = 0.045) and dogs aged ≥ 12 years (OR, 0.26; 95% CI, 0.11–0.58; P = 0.001) had reduced odds of surgical management (relative to non-surgical management) compared with dogs < 3 years. Increasing adult bodyweight was associated with increased odds of surgery, with dogs ≥ 30 kg at 2.19 times the odds (95% CI, 1.30–3.77; P = 0.004) of surgery compared with dogs < 10 kg. Insured dogs had 2.79 (95% CI, 2.01–3.89; P < 0.001) times the odds of surgery compared with uninsured dogs (Fig. 3). Dogs with one non-orthopaedic comorbidity at diagnosis had 0.38 times the odds of surgery (95% CI, 0.20–0.72; P = 0.003) compared with dogs with no comorbidity. The Hosmer-Lemeshow test indicated no evidence of poor model fit (P = 0.278) and the area under ROC curve (0.747) indicated acceptable ability to differentiate surgical and non-surgical cases.

Discussion

This is the largest study to date exploring risk factors for unilateral CCL rupture diagnosis in dogs under primary veterinary care, utilising EHR data from across the UK. Additionally, it is the first study epidemiologically exploring factors associated with clinical management of unilateral CCL rupture. Rottweiler, Bichon Frise and West Highland White terrier, dogs aged 6 to < 9 years, male neutered and female neutered dogs, and insured dogs all had increased odds of unilateral CCL rupture diagnosis. Insured dogs and dogs ≥ 20 kg had increased odds of surgical relative to non-surgical management, while dogs ≥ 9 years and dogs with one non-orthopaedic comorbidity at diagnosis had reduced odds. The analyses provide a thorough examination of associative factors and may be used to inform the development of prognostic models. We caution against interpreting them as causal effects, as some of the other variables included may act as mediators of the effects of the other variables.

The breeds identified at increased risk of unilateral CCL rupture, compared with crossbreeds, in the current study were the Rottweiler, Bichon Frise, West Highland White terrier, Golden retriever, Yorkshire terrier and Jack Russell terrier. These breed predispositions are largely in line with previous reports, although smaller, terrier-type breeds appear over-represented in the current study (Whitehair et al., 1993; Duval et al., 1999; Adams et al., 2011; Guthrie et al., 2012; Taylor-Brown et al., 2015; Engdahl et al., 2021). The Jack Russell terrier, which has not previously been identified at increased or decreased risk of CCL rupture, was identified as predisposed in the current study. This may reflect a true change in predisposition for this breed and could be related to the recent acceptance of the Jack Russell terrier as a Kennel Club (KC) recognised breed, allowing more standardisation of the phenotype (The Kennel Club, 2022). However, it could be that previous studies were

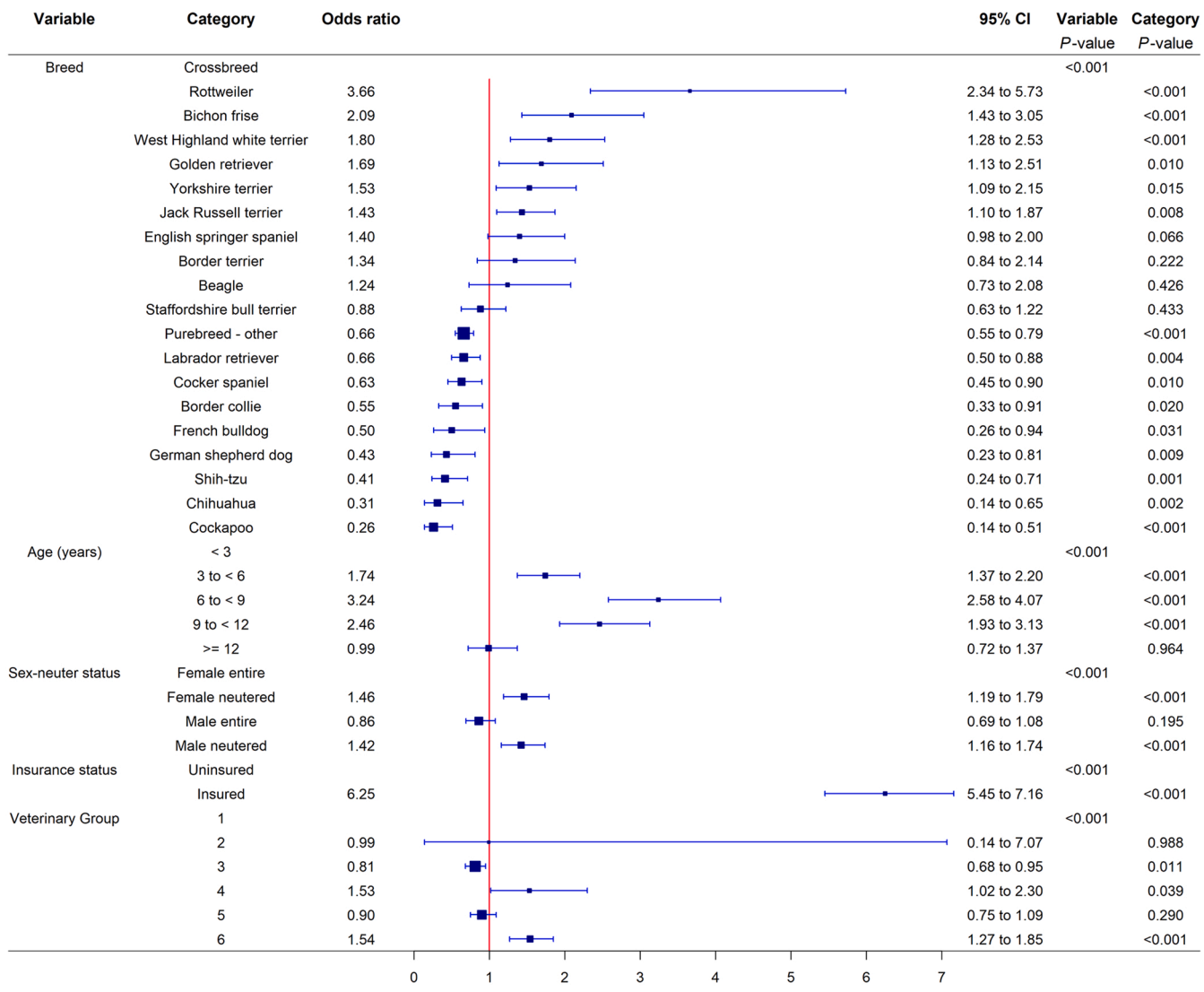

Fig. 1. Forest plot of the multivariable logistic regression odds ratios with corresponding 95% CIs (confidence intervals) for demographic risk factors associated with diagnosis of unilateral cranial cruciate ligament rupture in dogs under primary veterinary care in the UK (cases = 1000; non-cases = 500,000). Categories without an odds ratio were the baseline.

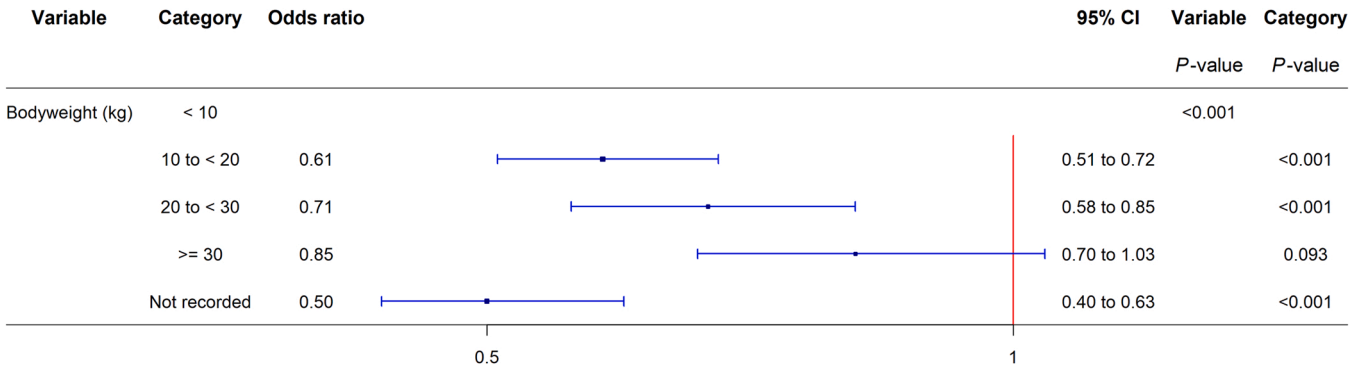

Fig. 2. Forest plot of the multivariable logistic regression odds ratios with corresponding 95% CIs (confidence intervals) for adult bodyweight as a risk factor for unilateral cranial cruciate ligament rupture diagnosis in dogs attending primary-care veterinary practices in the UK. This variable individually replaced the breed variable in the original multivariable logistic regression modelling (cases = 1000; non-cases = 500,000). The category without an odds ratio (<10 kg) was the baseline.

Table 2
Relative number (% of total; n = 1000) of unilateral cranial cruciate ligament (CCL) rupture cases managed surgically (n = 684) and non-surgically (n = 239) across a range of demographic and clinical variables in dogs attending primary-care veterinary practices in the UK.

Variable	Category	Management of CCL rupture	
		Surgical (%)	Non-surgical (%)
Breed	Crossbred	191 (27.9)	65 (27.2)
	Purebred - other	195 (28.5)	58 (24.3)
	Labrador retriever	48 (7.0)	6 (2.5)
	Jack Russell terrier	41 (6.0)	24 (10.0)
	West Highland White terrier	26 (3.8)	13 (5.4)
	Staffordshire bull terrier	30 (4.4)	8 (3.3)
	Golden retriever	24 (3.5)	3 (1.3)
	English springer spaniel	24 (3.5)	9 (3.8)
	Cocker spaniel	23 (3.4)	12 (5.0)
	Yorkshire terrier	22 (3.2)	12 (5.0)
	Bichon Frise	21 (3.1)	8 (3.3)
	Rottweiler	15 (2.2)	4 (1.7)
	Border collie	12 (1.8)	4 (1.7)
	Border terrier	10 (1.5)	8 (3.3)
	Chihuahua	2 (0.3)	5 (2.1)
Age (years)	< 3	82 (12.0)	18 (7.5)
	3 to < 6	162 (23.7)	32 (13.4)
	6 to < 9	282 (41.2)	75 (31.4)
	9 to < 12	136 (19.9)	78 (32.6)
	≥ 12	19 (2.8)	33 (13.8)
Bodyweight (kg)	< 10	150 (21.9)	88 (36.8)
	10 to < 20	183 (26.8)	63 (26.4)
	20 to < 30	131 (19.2)	31 (13.0)
	≥ 30	138 (20.2)	27 (11.3)
	Not recorded	82 (12.0)	30 (12.6)
Sex-neuter status	Female entire	108 (15.8)	38 (15.9)
	Female neutered	228 (33.3)	79 (33.1)
	Male entire	111 (16.2)	48 (20.1)
	Male neutered	237 (34.6)	74 (31.0)
Insurance status	Uninsured	196 (28.7)	131 (54.8)
	Insured	488 (71.3)	108 (45.2)
Veterinary Group	1	193 (28.2)	59 (24.7)
	3	220 (32.2)	76 (31.8)
	4	19 (2.8)	7 (2.9)
	5	131 (19.2)	36 (15.1)
	6	121 (17.7)	61 (25.5)
Body condition status[a]	Overweight/obese	191 (27.9)	87 (36.4)
	Ideal bodyweight	56 (8.2)	28 (11.7)
	Underweight	0 (0.0)	0 (0.0)
	Not recorded	437 (63.9)	124 (51.9)
Orthopaedic comorbidity at diagnosis	No recorded comorbidity	461 (67.4)	178 (74.5)
	Osteoarthritis	158 (23.1)	45 (18.8)
	Patella luxation	30 (4.4)	11 (4.6)
	Hip dysplasia	31 (4.5)	4 (1.7)
	Coxofemoral disease treated by total hip replacement	2 (0.3)	2 (0.3)
	Lumbar spondylitis	1 (0.1)	1 (0.1)
	Fracture	1 (0.1)	0 (0.0)
Number of non-orthopaedic comorbidities at diagnosis	0	655 (95.8)	207 (86.6)
	1	27 (3.9)	28 (11.7)
	2	1 (0.1)	2 (0.8)
	3	1 (0.1)	2 (0.8)

[a] Body condition status was derived following review of clinical information contained within the electronic health record

insufficiently powered to detect an association. The cockapoo, Chihuahua, Shih-Tzu, German shepherd dog, French bulldog, Border collie, Cocker spaniel, and Labrador retriever were identified at decreased risk of unilateral CCL rupture in the current study. Focusing on breed protection, rather than just predisposition, has been a recent shift within companion animal epidemiology (Pegram et al., 2020), providing evidence that can support moves to select towards positive features as well as away from negative features (The Kennel Club, 2019; Pegram et al., 2020; O'Neill et al., 2021b).

The median age at first CCL rupture diagnosis was 7.4 years, which is in line with the value of 7.0 years reported in a previous report based on primary-care data in England (Taylor-Brown et al., 2015). In the current study, dogs aged 6 to < 9 years had greatest risk of CCL rupture (OR, 3.24) compared with dogs < 3 years. This differs slightly to the report based on primary-care data in England in which dogs aged 9 to < 12 years were at greatest risk (Taylor-Brown et al., 2015). This suggests that the age at first CCL rupture diagnosis may be decreasing, however the current study included incident cases only, while the previous study included both incident and pre-existing cases, which could account for the difference. The current study included absolute age, rather than lifespan. Life tables of annual life expectancy and mortality for common dog breeds in the UK have recently been developed (Teng et al., 2022) and could be used in future studies where lifespan is of primary interest.

Female and neutered dogs have previously been identified at increased risk of CCL rupture (Whitehair et al., 1993; Duval et al., 1999; Witsberger et al., 2008; Taylor-Brown et al., 2015; Engdahl et al., 2021). Female neutered dogs were at greatest risk of unilateral CCL rupture compared with female entire dogs in the current study (OR, 1.46). However, the risk of unilateral CCL rupture in male neutered dogs (OR, 1.42) was very similar to the risk in female neutered dogs, while the risk in male entire dogs did not significantly differ to the risk in female entire dogs, indicating neuter status as the predominant factor. The pathophysiology behind a link between neutering and CCL rupture is unclear, but an explanatory association between neutering, obesity, and CCL rupture has been suggested (Witsberger et al., 2008; Taylor-Brown et al., 2015).

Insured dogs had 6.25 (95% CI, 5.45–7.16) times the odds of unilateral CCL rupture diagnosis compared with uninsured dogs, higher than the odds of 4.00 (95% CI, 3.2–4.9) reported in a previous study based on primary-care data in England (Taylor-Brown et al., 2015). This may reflect more prompt evaluation and thorough clinical investigation in insured dogs (Egenvall et al., 2009; Taylor-Brown et al., 2015), with the odds possibly increasing as the level of veterinary care has advanced (Quain et al., 2021), although may also reflect that CCL rupture cases are more likely to have their insurance status recorded in the EMR.

Dogs considered overweight have been reported at increased risk of CCL rupture (Whitehair et al., 1993; Duval et al., 1999; Santarossa et al., 2020;). Leptin, a proinflammatory adipocytokine, has been correlated with body condition score (BCS) in dogs (Kleine et al., 2019). A negative

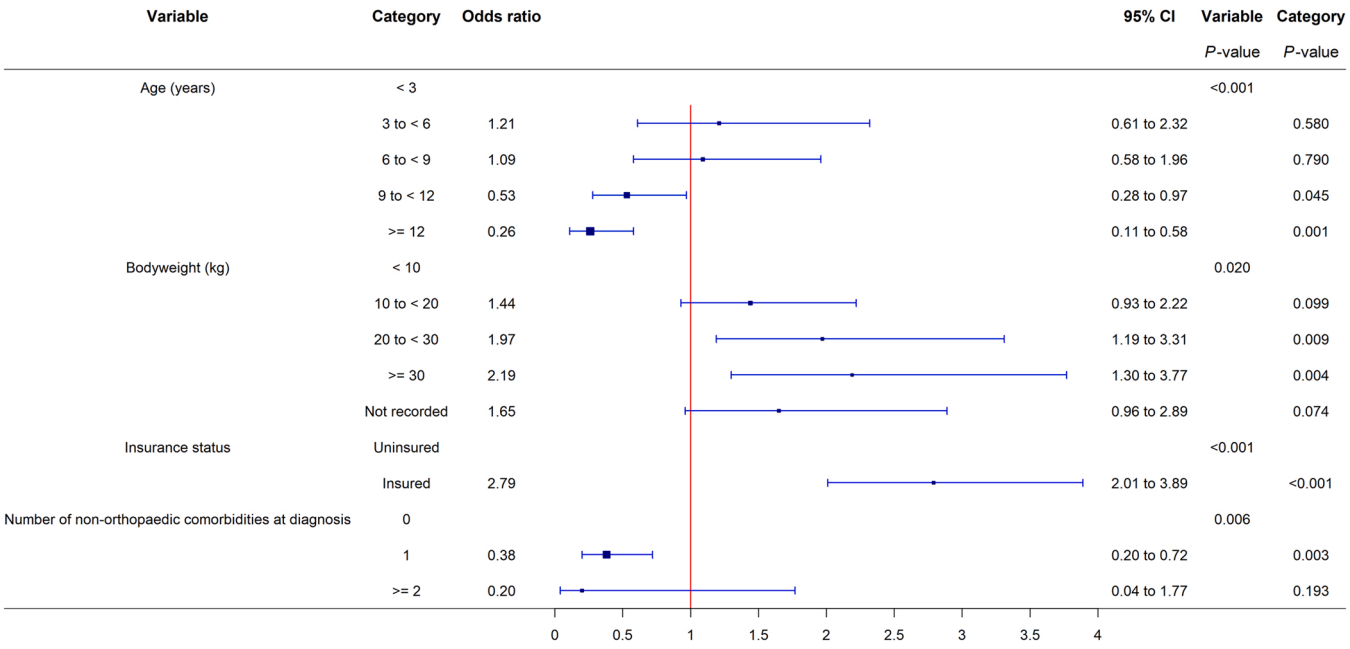

Fig. 3. Forest plot of the multivariable logistic regression odds ratios with corresponding 95% CIs (confidence intervals) for risk factors associated with surgical (n = 684) versus non-surgical management (n = 239) of unilateral cranial cruciate ligament rupture in dogs under primary veterinary care in the UK. Categories without an odds ratio were the baseline.

impact of leptin on chondrocyte health has been reported, therefore an association between excessive body condition, leptins, and CCL rupture has been suggested (Adams et al., 2011). Data on body condition status was not available for non-cases, although bodyweight relative to the breed-sex median (which represents a loose proxy for body condition status) was not significantly associated with CCL rupture diagnosis in multivariable modelling. However, there can be within-breed variation in size and there is limited evidence for a 'reference standard' bodyweight by breed, sex, and age (Pegram et al., 2021b). Given that prevalence for overweight body condition status recorded in dogs under primary veterinary care has been reported as 7.1% (Pegram et al., 2021b), the overweight prevalence of 27.9% in dogs treated surgically and 36.4% in dogs treated non-surgically in the current study supports previous reports that overweight dogs are more likely to be diagnosed with CCL rupture (Whitehair et al., 1993; Duval et al., 1999; Santarossa et al., 2020).

Increasing absolute bodyweight has been reported as a risk factor for CCL rupture in dogs (Whitehair et al., 1993; Duval et al., 1999; Taylor-Brown et al., 2015; Santarossa et al., 2020;). The current study identified dogs 10 to < 20 kg and 20 to < 30 kg at reduced risk of unilateral CCL rupture compared with dogs < 10 kg. Given that four of the six predisposed breeds in the current study were small-breed dogs (Bichon Frise, West Highland White terrier, Yorkshire terrier, and Jack Russell terrier), it is possible that breed, rather than bodyweight, is the more important driving factor. Although a single genetic cause for CCL rupture has not been determined (Cook, 2010), the increased risk of unilateral CCL rupture in small-breed dogs, and particularly in terrier breeds, in the current study warrants further investigation. However, individual breeds were only included if there were at least 15 cases, meaning that predispositions in rare breeds were less likely to be identified.

Based on previous evidence (Comerford et al., 2013; Taylor-Brown et al., 2015), the current study hypothesized that higher bodyweight in dogs with unilateral CCL rupture is associated with increased odds of surgical management relative to non-surgical management. The current results support this hypothesis, with dogs 20 to < 30 kg at 1.97 times the odds and dogs ≥ 30 kg at 2.19 times the odds of surgical management, relative to non-surgical management, compared with dogs < 10 kg. Although there is some historic evidence that dogs weighing 15 kg or less can be successfully managed non-surgically (Pond and Campbell, 1972; Vasseur, 1984), a recent narrative literature review concluded that there was some evidence, albeit limited, that non-surgical management results in prolonged recovery time compared with surgical management in dogs < 15 kg (Brioschi and Arthurs, 2021). Given the limited evidence-base, further research exploring the clinical outcomes of dogs managed surgically compared with non-surgically is warranted, to help guide veterinarian-owner decision-making.

Younger CCL rupture cases were more likely to receive surgical management than older CCL rupture cases. Dogs aged 9 to < 12 years were at 0.53 times the odds and dogs ≥ 12 years at 0.26 times the odds of surgical management, relative to non-surgical management, compared with dogs < 3 years. Risk of anaesthetic death increases with age (Brodbelt et al., 2008; Shoop-Worrall et al., 2022), therefore veterinarians may have been more cautious in recommending surgery in older dogs if non-surgical management was an option. Further studies exploring the outcome of non-surgical management in older dogs would help guide this decision-making.

General health in CCL rupture cases appeared to play an important role in whether CCL rupture cases received surgical management. Dogs with one or more non-orthopaedic comorbidity at time of CCL rupture diagnosis were at 0.38 times the odds of surgical management, relative to non-surgical management, compared with dogs with no comorbidity. As very few dogs in the study had two or more non-orthopaedic comorbidities at diagnosis (n = 6) analysis was insufficiently powered to be able to detect any association with management. Veterinarians in practice are advised to use The American Society of Anesthesiologists (ASA) physical status (PS) classification system to assess a dog's physical status, which incorporates comorbidities (Portier and Ida, 2018). A higher ASA PS is associated with an increased risk of anaesthetic death (Brodbelt et al., 2008; Portier and Ida, 2018; Shoop-Worrall et al., 2022). Therefore, as with older dogs, veterinarians and owners may approach the decision to surgically operate with more caution.

Insured dogs were at 2.79 times the odds of surgical management, relative to non-surgical management, compared with uninsured dogs. Surgery for CCL rupture can be expensive, with a US study reporting the mean cost for a single specialist CCL surgery as $1840.50 (compared to

$241.20 for non-surgical management; Wilke et al., 2005; Toth and Siegel, 2021), suggesting that a surgical option for an uninsured dog may not always be a financially viable option. The current study highlights that insurance status is more strongly associated with the diagnosis of unilateral CCL rupture (OR, 6.25) than the clinical management (OR, 2.79), suggesting a commitment to surgical management from owners opting for a diagnosis, regardless of insurance status. However, more accurate recording of insurance status in dogs diagnosed with CCL rupture may also play a part.

The limitations of this study mirror previous VetCompass publications that use similar methods, and largely reflect the retrospective analysis of EMR data (O'Neill et al., 2014). Given insured dogs had 6.25 times the odds of CCL rupture diagnosis compared with uninsured dogs, it is possible there were many uninsured dogs with true CCL rupture that went undiagnosed, resulting in misclassification bias. However, dogs were excluded from the non-case group that had any of the CCL-specific search terms within their records.

Additional factors, such as severity and duration of clinical signs, dog behaviour, and lifestyle, might also affect the management of CCL rupture, but information on these factors was not included in the current analyses. Future prospective studies might evaluate the influence of such additional factors, although retrospective primary-care data may be a relatively poor source of this type of information.

Conclusions

This is the largest epidemiological study to date on unilateral CCL rupture in the UK dog population. Six risk factors were associated with diagnosis of unilateral CCL rupture: breed, age, adult bodyweight, sex-neuter status, insurance status, and veterinary group. Rottweiler, Bichon Frise, West Highland White terrier, Golden retriever, Yorkshire terrier, and Jack Russell terrier breeds were predisposed to CCL rupture compared with crossbreeds. Four risk factors were associated with clinical management of CCL rupture: age, adult bodyweight, insurance status, and presence of non-orthopaedic comorbidities at diagnosis. These findings inform identification of at-risk dogs, with an apparent shift towards smaller breeds. Additionally, they highlight the clinical rationales used in primary-care veterinary practices to decide between surgical or non-surgical management of unilateral CCL rupture. Further prospective studies evaluating clinical outcomes will help demonstrate whether these rationales are valid.

Conflict of interest statement

None of the authors has any financial or personal relationships that could inappropriately influence or bias the content of the paper.

Acknowledgments

The authors are grateful to Dogs Trust for their funding of this research. Thanks to Noel Kennedy (RVC) for VetCompass software and programming development. We acknowledge the Medivet Veterinary Partnership, Vets4Pets/Companion Care, Goddard Veterinary Group, CVS Group, IVC Evidensia, Linnaeus Group, Beaumont Sainsbury Animal Hospital, PDSA, Blue Cross, Dogs Trust, Vets Now, and the other UK practices who collaborate in VetCompass. We are grateful to The Kennel Club Charitable Trust, Agria Pet Insurance, and The Kennel Club for supporting VetCompass.

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