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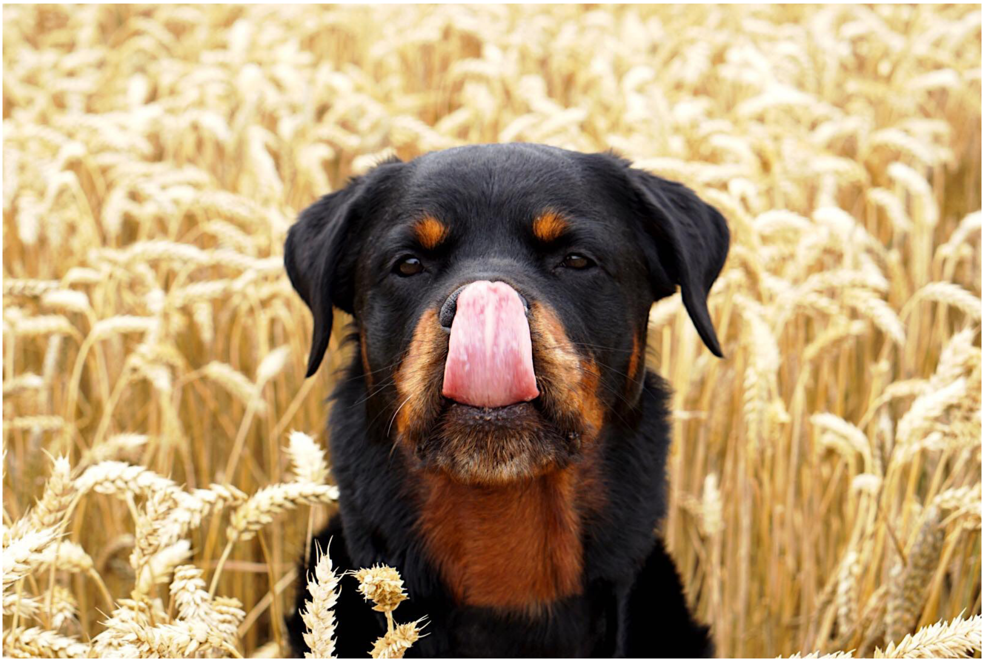
The epidemiology of stifle joint disease in dogs

with a focus on cranial cruciate ligament disease

Karolina Engdahl



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Cover: Rottweiler, a breed at high risk of cranial cruciate ligament disease
(photo: Lisa Gustafsson)

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Abstract

Stifle joint disease (SJD) is common in dogs and comprises many diagnoses, of which cruciate ligament disease (CLD) is often reported as the most prevalent. Several treatment options are available for CLD, but there is no consensus on which treatment yields the best results. The aims of this thesis were to investigate the epidemiology of SJD in dogs, with a focus on CLD, and to evaluate outcomes in dogs after treatment for CLD.

Data from Agria Pet Insurance was used to evaluate risk factors for SJD and CLD. The diseases affected breeds of all sizes, although larger breeds, especially molosser types, were overrepresented among those at high risk of CLD. An association between breed size and age at CLD diagnosis was observed: most breeds diagnosed at younger ages were large or giant, while most that were older at diagnosis were small. Seven large breeds also had an increased risk of euthanasia due to CLD.

Outcome assessments after treatment for CLD included evaluation of severe postoperative complications and survival in dogs diagnosed with CLD at two university animal hospitals. Severe postoperative complications occurred in 25.1% of surgically treated stifles. Stifles treated with tibial plateau levelling osteotomy had a significantly lower hazard of severe postoperative complications than those treated with lateral fabellotibial suture. The hazard also decreased with increasing age and increased with increasing body weight. The median survival from treatment initiation to CLD-related euthanasia was 1.3 years. Dogs treated with osteotomy procedures had a significantly lower hazard of CLD-related euthanasia than conservatively treated dogs. The hazard increased with increasing age and body weight, and was higher for dogs with concurrent orthopaedic comorbidities.

Keywords: knee joint, TPLO, TTA, LFS, MMP, conservative, survival analysis, canine, patellar luxation, orthopaedic disease.

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Knäledssjukdomarnas epidemiologi hos hund

Sammanfattning

Knäledssjukdomar är vanligt förekommande hos hund och inkluderar många diagnoser, där korsbandsskada (KS) ofta rapporteras som den vanligaste. Det finns flera behandlingsalternativ för KS, men det råder ingen konsensus om vilken behandling som ger bäst resultat. Målet med avhandlingen var att undersöka knäledssjukdomarnas epidemiologi hos hund, med fokus på KS, samt att utvärdera behandlingsresultatet för hundar med KS.

Data från Agria Djurförsäkring användes för att utvärdera riskfaktorer för knäledsjukdom och KS. Sjukdomarna drabbade raser av alla storlekar, även om stora raser, särskilt av molossertyp, var överrepresenterade bland raserna med hög risk för KS. En association mellan rasstorlek och ålder vid KS-diagnos påvisades: de flesta raser som var yngre vid diagnos var stora, medan raserna som var äldre vid diagnos generellt var små. Sju stora raser hade ökad risk för avlivning på grund av KS.

Utvärderingen av behandlingsresultat inkluderade analys av allvarliga postoperativa komplikationer och överlevnad hos hundar diagnosticerade med KS vid två universitetsdjursjukhus. Totalt drabbades 25,1% av de opererade knälederna av allvarliga postoperativa komplikationer. Knälederna behandlade med tibial plateau levelling osteotomy hade signifikant lägre risk att drabbas jämfört med de som behandlats med lateral fabellotibial sutur. Dessutom minskade risken med stigande ålder och ökade med ökande kroppsvikt. Medianöverlevnaden från behandlingsstart till KS-relaterad avlivning var 1,3 år. Hundar behandlade med osteotomitekniker hade signifikant lägre risk att avlivas på grund av KS. Dessutom ökade risken med stigande ålder och ökande kroppsvikt och var högre för hundar med andra ortopediska sjukdomar.

Nyckelord: knäled, TPLO, TTA, LFS, MMP, konservativ behandling, överlevnadsanalys, patellaluxation, ortopedisk sjukdom

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Dedication

To Bob Hund, who stood constantly by my side (literally) as I wrote this thesis.

'Being an athlete is a well-known risk factor for cruciate-ligament injury. A larger – but lesser-known – risk factor is being a dog.'
Kevin Helliker, April 11, 2006, The Wall Street Journal

Contents

List of publications

This thesis is based on the work contained in the following papers, referred to by Roman numerals in the text:

I. Engdahl, K., Hanson, J., Bergström, A., Bonnett, B., Höglund, O., Emanuelson, U. (2021). The epidemiology of stifle joint disease in an insured Swedish dog population. Veterinary Record, Vol 189 189 (3), p. e197.

II. Engdahl, K., Emanuelson, U., Höglund, O., Bergström, A., Hanson, J. (2021). The epidemiology of cruciate ligament rupture in an insured Swedish dog population. Scientific Reports, Vol 11 (1).

III. Engdahl, K.*, Boge, G.S.*, Bergström, A., Moldal, E.R., Höglund, O. (2021). Risk factors for severe postoperative complications in dogs with cranial cruciate ligament disease – a survival analysis. Preventive Veterinary Medicine, Vol 191, p. 105350.

IV. Boge, G.S.*, Engdahl, K.*, Bergström, A., Emanuelson, U., Hanson, J., Höglund, O., Moldal, E.R., Skjerve, E., Krontveit, R. (2020). Disease-related and overall survival in dogs with cranial cruciate ligament disease, a historical cohort study. Preventive Veterinary Medicine, Vol 181, p.105057.

*Authors contributed equally to these works.

Karolina Engdahl contributed to the papers included in this thesis as follows:

I. Karolina Engdahl performed the statistical analyses under supervision from Ulf Emanuelson, Jeanette Hanson, and Brenda Bonnett, and drafted the manuscript. All authors contributed to the study design, interpretation of the results, and revision of the manuscript.

II. Karolina Engdahl performed the statistical analyses under supervision from Ulf Emanuelson and Jeanette Hanson, and drafted the manuscript. All authors contributed to the study design, interpretation of the results, and revision of the manuscript.

III. Karolina Engdahl and Gudrun Seeberg Boge collected the data, performed the statistical analyses, and drafted the manuscript. All authors contributed to the study design, interpretation of the results, and revision of the manuscript.

IV. Karolina Engdahl and Gudrun Seeberg Boge collected the data, performed the statistical analyses under supervision from Randi Krontveit, and drafted the manuscript. All authors contributed to the study design, interpretation of the results, and revision of the manuscript.

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Abbreviations

CCL	Cranial cruciate ligament
CCLD	Cranial cruciate ligament disease
CLD	Cruciate ligament disease
DYAR	Dog-years at risk
IR	Incidence rate
LFS	Lateral fabellotibial suture
OA	Osteoarthritis
PL	Patellar luxation
RR	Relative risk
SJD	Stifle joint disease
SSI	Surgical site infection
TPLO	Tibial plateau levelling osteotomy
TTA	Tibial tuberosity advancement

1. Introduction

Dogs are popular companion animals in Sweden; during 2012 it was estimated that around 13% of all households had a dog (Statistics Sweden, 2012). Dogs are kept for many purposes, including hunting, herding, guarding, rescue, assistance, therapy, and company. Dogs suffer from a variety of diseases that can affect all their organ systems. Disorders of the musculoskeletal system, including diseases affecting joints, bones, muscles, ligaments, and tendons, are among the most common diseases in dogs brought to veterinary practices (O'Neill *et al.*, 2021; O'Neill *et al.*, 2014). Stifle joint disease (SJD) accounts for a large proportion of these cases (Johnson *et al.*, 1994). The stifle joint is an important part of a dog's locomotor apparatus, and dysfunction of the joint can result in severe locomotor impairment, with associated pain and lameness.

1.1 The stifle joint in dogs

1.1.1 Anatomy and function

The stifle is a complex synovial joint comprising several anatomical structures. It contains three freely communicating joint compartments: the femoropatellar, femorotibial, and proximal tibiofibular joints (Dyce *et al.*, 2010). The joint surface of the femur consists of two condyles separated by a deep intercondylar fossa, while the joint surface of tibia, the tibial plateau, consists of two condyles separated caudally by a popliteal notch (Dyce *et al.*, 2010).

The stifle joint is stabilized by several ligaments. The collateral ligaments, located on the medial and lateral aspects of the joint, act as restraints to prevent varus and valgus angulation as well as internal and external rotation of the tibia (Dyce *et al.*, 2010; Vasseur & Arnoczky, 1981). The cranial cruciate ligament (CCL) emanates from the caudomedial part of the lateral femoral condyle and inserts on the cranial intercondylar region of the tibial plateau (Figure 1). The ligament consists of two bands, one craniomedial and one caudolateral, with complicated structural and functional relationships (Arnoczky & Marshall, 1977). The caudal cruciate ligament arises within the intercondylar fossa on the lateral aspect of the medial femoral condyle and inserts on the lateral edge of the popliteal notch of the tibia (Arnoczky & Marshall, 1977).

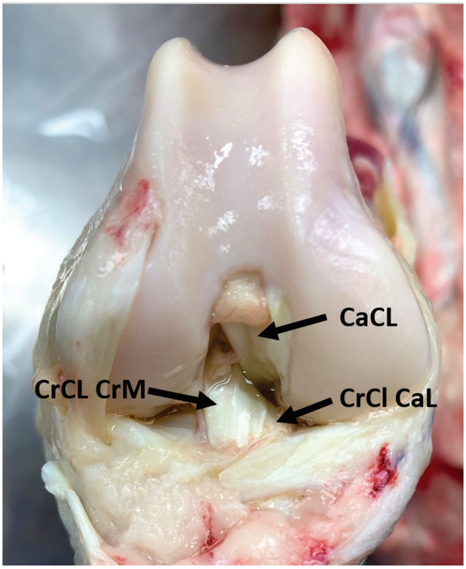


Figure 1. Anatomy of the cruciate ligaments. *CaCL* caudal cruciate ligament, *CrCL CrM* cranial cruciate ligament, craniomedial band, *CrCL CaL* cranial cruciate ligament, caudolateral band. Photo: Karolina Engdahl.

The CCL prevents hyperextension of the stifle joint, extensive cranial movement of the tibia relative to the femur, and internal rotation of tibia (Arnoczky & Marshall, 1977). The ligament is covered by a layer of synovial membrane, which makes it intra-articular but extra-synovial (Vasseur *et al.*, 1985). Approximately two thirds of the ligament consists of water; 75% of the ligament's dry weight is the protein collagen, and the rest consists of proteoglycans, elastin, and other proteins (Carlson & Weisbrode, 2011). The most common type of collagen in the ligament is type I, which is produced by fibroblasts (Carlson & Weisbrode, 2011). The collagen is organized in a wave formation called crimp; loading likely results in some areas of the ligament uncrimping, allowing it to extend without damage (Carlson & Weisbrode, 2011).

Two fibrocartilaginous menisci, which are wedge-shaped in section and semilunar in plan, fill the space between the incongruent articular surfaces of the femur and tibia (Dyce *et al.*, 2010). The menisci absorb kinetic energy, contribute to joint stability, and lubricate the joint (Schulz, 2013).

The patella, a sesamoid bone located in the trochlear groove of the femur, attaches to the tibial tuberosity via the patellar ligament (Dyce *et al.*, 2010). The patella and the patellar ligament are important parts of the stifle's extensor mechanism, together with the quadriceps femoris muscle, femoral trochlea, and tibial tuberosity (McKee & Cook, 2006).

1.1.2 Biomechanics

The stifle functions as a hinge joint that is flexed in standing position (Dyce *et al.*, 2010). The motion of the joint is mostly restricted to flexion and extension, although some internal and external rotation is possible (Arnoczky & Marshall, 1977). The joint is affected both by external ground forces and internal muscle-generated forces during motion (McKee & Cook, 2006). These forces result in a cranially oriented shear force on the tibia called 'cranial tibial thrust' (Slocum & Devine, 1983). This shear force is generated by the slope of the tibial plateau, which is oriented caudodistally instead of perpendicular to a line joining the centres of motion of the stifle and hock joints (Slocum & Devine, 1983). The CCL usually passively resists this shear force (Arnoczky & Marshall, 1977).

1.1.3 The importance of stifle joint disease in dogs

Stifle joint disease comprises a variety of diagnoses, such as cranial cruciate ligament disease (CCLD), patellar luxation (PL), osteoarthritis (OA), and osteochondrosis, of which CCLD and PL are the most commonly reported (O'Neill *et al.*, 2021; Wolf *et al.*, 2020; Wiles *et al.*, 2017; Johnson *et al.*, 1994). The disorders occur at different life stages: PL and osteochondrosis are developmental diseases, with clinical signs that often debut at a young age; CCLD and OA are degenerative diseases that generally debut in middle-aged to older dogs (Anderson *et al.*, 2018; O'Neill *et al.*, 2016; Taylor-Brown *et al.*, 2015; Nečas *et al.*, 1999). Osteoarthritis may occur as a primary disease, but can also develop and progress to a chronic condition in stifle joints affected by diseases such as CCLD and PL (Anderson *et al.*, 2020).

Stifle joint diseases affect dogs of all sizes: PL is commonly reported in small breeds, while CCLD and OA tend to affect larger breeds, although they may affect breeds of all sizes (Anderson *et al.*, 2018; O'Neill *et al.*, 2016; Taylor-Brown *et al.*, 2015; Witsberger *et al.*, 2008; Whitehair *et al.*, 1993). These diseases cause varying degree of lameness, ranging from mild to severe (Muir, 2018; Alam *et al.*, 2007). Several treatment options are available for the different SJDs, some of which involve a complicated surgical procedure with high associated costs. For example, it was estimated that in 2003 the total cost of treatment for CCLD in dogs in the US was $1.32 billion (Wilke *et al.*, 2005).

Chronic diseases such as OA are an obvious animal welfare problem, but are also associated with higher levels of caregiver burden, stress, symptoms of depression and anxiety, and poorer quality of life in the animal owner (Anderson *et al.*, 2018; Spitznagel *et al.*, 2017). Orthopaedic disease is a common reason for euthanasia in dogs. Musculoskeletal disorders were the second most common cause of death/euthanasia in juvenile and adult dogs in North America during 1984 to 2004, and were the reason for 5.9% of dog euthanasia at primary veterinary practices in England in 2016 (Pegram *et al.*, 2021; Fleming *et al.*, 2011). In Sweden, around 10% of all deaths reported to the insurance company Agria Pet Insurance during 1992 and 1993 were related to locomotor problems (Bonnett *et al.*, 1997). Further, cruciate ligament disease (CLD) was the fifth most common reason for death/euthanasia among dogs with life insurance settlements due to locomotor disease during 1995 to 2000 (Bonnett *et al.*, 2005). The decision to euthanize is often complex. Factors that contribute to the decision in patients with SJD are not well explored, but may include treatment failure, severe surgical complications, chronic pain, unacceptable dysfunction in working dogs, and the dog owner’s inability to afford treatment.

In summary, the majority of SJDs are chronic, affect dogs of all ages and sizes, and often involve a surgical treatment with high associated costs. Investigation of disease’s aetiopathogenesis, risk factors, and optimal treatment methods is crucial for preventing disease and optimizing treatment outcomes.

1.2 Cranial cruciate ligament disease

1.2.1 Response to injury

Rupture of the CCL allows cranial movement of the tibia, resulting in stifle joint instability (Arnoczky & Marshall, 1977). A ten millimetre increase in tibial cranial translation during the stance phase has been observed after experimental transection of the cruciate ligament (Tashman *et al.*, 2004). Factors such as biomechanical forces, nutritional delivery, complex ligament anatomy, and biological environment can affect the healing capacity of the CCL negatively (Chamberlain *et al.*, 2018). Generally, ruptured ligaments go through three phases during the healing process: the inflammatory phase, the proliferative phase, and the remodelling phase (Carlson & Weisbrode, 2011; Chamberlain *et al.*, 2009). The inflammatory phase involves the formation of a hematoma at the site of the rupture (Carlson & Weisbrode, 2011). Inflammatory cells are recruited to resorb debris and fibroblasts are attracted to synthesize extracellular matrix from inflammation through the proliferative phase (Carlson & Weisbrode, 2011). For an injured medial collateral ligament, the remodelling phase starts two to three weeks after the injury and involves the organization of collagen fibres in the longitudinal axis of the ligament to restore mechanical strength (Carlson & Weisbrode, 2011; Chamberlain *et al.*, 2009). However, the ligament remains inferior to a normal ligament (Chamberlain *et al.*, 2009). In contrast to the medial collateral ligament, the healing ability of a completely ruptured CCL is poor since a bridging scar does not form in the rupture site (Hayashi, 2018; Tirgari, 1978a). A partially ruptured ligament may heal to some degree, but the defect will remain incompletely filled and the ligament remains inferior to a normal ligament (O'Donoghue *et al.*, 1966).

Signs of concurrent inflammation such as thickened joint capsules and proliferative changes in the synovial membranes have been found in stifles affected by CCLD (Tirgari, 1978a). Synovia from the affected stifles usually shows signs of degenerative joint disease, including increased volume, discolouration, and increased mononuclear white blood cells (Bennett *et al.*, 1988; Tirgari, 1978a). Chronic degenerative changes have also been found in the ruptured ligaments (Tirgari, 1978a). It remains unknown whether the chronic degenerative process is initiated by pre-existing primary stifle joint synovitis or microtrauma to the cruciate ligament, resulting in in stifle joint instability and inflammation (Hayashi, 2018). Acute ruptures associated with trauma and no pre-existing degenerative process also occur, but are much more rare (Muir, 2018).

Degenerative changes in the CCL are not exclusively found in stifle joints with CCLD. One study reported that 44.6% of dogs euthanized for reasons unrelated to SJD had degenerative changes in their CCLs as well as varying degree of stifle joint synovitis (Doring *et al.*, 2018). A trend in small dogs of less severe degenerative changes and later onset than in large dogs has also been described (Vasseur *et al.*, 1985). The impact of these degenerative changes and why they occur is still unknown.

Concurrent or subsequent rupture of the contralateral CCL is common. Studies report that 4.3% to 10.6% of dogs with CCLD are affected by bilateral CCLD on admission and that subsequent rupture occurs in 34.4% to 54% of dogs presenting with unilateral CCLD (Grierson *et al.*, 2011; Muir *et al.*, 2011; Buote *et al.*, 2009). The mean or median time to contralateral rupture in dogs presenting with unilateral disease typically varies from 10.1 months to 2.6 years (Grierson *et al.*, 2011; Muir *et al.*, 2011; Buote *et al.*, 2009).

Concurrent meniscal injuries of several types (longitudinal, radial, bucket-handle, horizontal, caudal peripheral, and complex tears) are reported in up to 84.6% of dogs with CCLD that undergo arthrotomy or arthroscopy at time of stifle stabilization (Franklin *et al.*, 2018; McCready & Ness, 2016a). The medial meniscus lacks femoral attachment, which allows it to move cranially with the tibia during weight bearing (McKee & Cook, 2006). This can cause a damaging impingement of the meniscus between the medial femoral condyle and the tibial plateau, which makes that meniscus more vulnerable to injuries than the lateral meniscus. The healing ability of menisci is poor, due to poor blood supply (Tirgari, 1978b).

1.2.2 Clinical features and diagnostic methods

History and clinical examination

Dogs with CCLD usually present with clinical signs such as acute or gradual onset lameness, stifle joint pain, stiffness, and unsteady gait (Bennett *et al.*, 1988). Clinical examination may reveal muscle atrophy of the affected limb, stifle joint effusion, and a firm thickening of the medial aspect of the joint due to periarticular fibrosis, often called ‘medial buttress’ (Muir, 2018).

The cranial drawer test and/or the tibial compression test can be used to evaluate stifle joint instability in dogs with suspected CCL rupture (Figure 2; Schulz, 2013). The cranial drawer test is performed with the dog in lateral recumbency. One hand stabilizes the femur by placing the thumb on the lateral fabella and the index finger on the patella. The other hand grasps the tibia, with the thumb behind the fibular head and the index finger on the tibial crest, and forces the tibia in a cranial and caudal movement. The test should be performed with the joint in various degrees of extension/flexion. The tibial compression test is performed in lateral recumbency with extended stifle (Henderson & Milton, 1978). One hand holds the femoral condyles with the index finger placed along the patellar tendon to detect cranial instability, as the other hand flexes and extends the tarsal joint. It is important to examine both stifle joints as bilateral CCLD is common.

Both tests have limitations. The sensitivity to detect stifle joint instability in conscious patients has been reported to be 60% for the cranial drawer and 64% for the tibial compression test, increasing to around 90% for both tests in the anaesthetized patient (Carobbi & Ness, 2009). However, the sensitivity is likely affected by several factors, such as the experience of the examining veterinarian, the conformation of the dog, and the degree of ligament rupture.

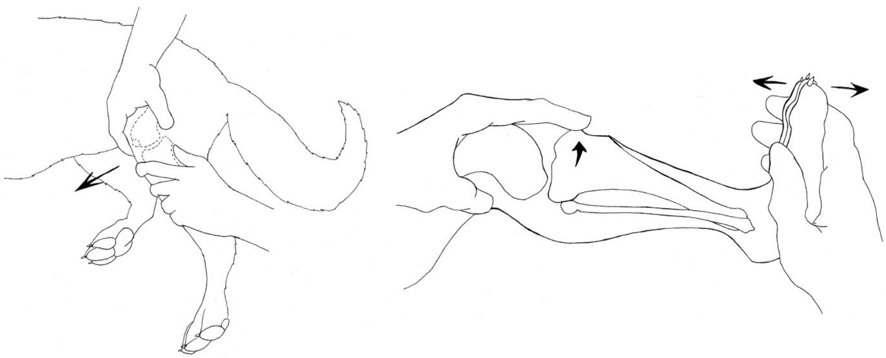


Figure 2. The tests used to diagnose cranial cruciate ligament disease. Left: the cranial drawer; Right: the tibial compression test. Illustrations: Johan Bergdahl.

Diagnostic imaging

Radiographs are often included in the clinical evaluation of dogs with suspected CCLD. Although the cruciate ligaments cannot be visualized on radiographs, an exaggerated cranial position of the tibia in relation to the femur indicates CCL rupture (Kim, 2018). In addition, concurrent signs of OA, such as synovial effusion and osteophytosis, are usually present in stifle joints affected by CCLD (Ashour *et al.*, 2019; Au *et al.*, 2010; Lazar *et al.*, 2005). These changes are nonspecific, however, and can be associated with diseases other than CCLD. Radiographic signs of joint effusion and osteophytosis are commonly encountered in the contralateral stifle joint at time of CCLD diagnosis in the index stifle (Chuang *et al.*, 2014).

1.2.3 Epidemiology

Disease prevalence

The reported prevalence of CCLD in dogs varies from 0.56% to 2.55% (O'Neill *et al.*, 2021; Taylor-Brown *et al.*, 2015; Adams *et al.*, 2011; Witsberger *et al.*, 2008). This variation is likely a result of differences in study design, study population, and study location. Witsberger *et al.* (2008) evaluated change in CCLD prevalence in the Veterinary Medical Database in the US from 1964 to 2003, and concluded that the disease prevalence increased from 1.81% in the first ten year period (1964–1973) to 4.87% in the last (1994–2003). The authors suggested that the increase was due to increased veterinarian recognition of the disease, rather than increased underlying frequency of CCLD.

Age

The reported mean and median ages at CCLD diagnosis vary from 4.3 to 8.1 years (O'Neill *et al.*, 2021; Boge *et al.*, 2019; Taylor-Brown *et al.*, 2015; Guthrie *et al.*, 2012; Adams *et al.*, 2011; Harasen, 2008; Necas *et al.*, 2000). High age has been reported as a risk factor for CCLD (Taylor-Brown *et al.*, 2015; Witsberger *et al.*, 2008; Whitehair *et al.*, 1993). For example, Taylor-Brown *et al.* (2015) reported that dogs aged 9 to 11.9 years had 4.4 times the odds of a CCLD diagnosis than dogs aged under three. Information on breed-specific age at diagnosis is limited, but an association between decreasing age and increasing body weight at diagnosis has been described, suggesting that larger dogs seem to be affected by CCLD earlier in life than smaller dogs (Harasen, 2008; Duval *et al.*, 1999; Whitehair *et al.*, 1993).

Breed

The Rottweiler is reported to be at high risk of CCLD in most studies that evaluate breed as a risk factor for CCLD (Figure 3; Boge *et al.*, 2019; Wiles *et al.*, 2017; Taylor-Brown *et al.*, 2015; Adams *et al.*, 2011; Witsberger *et al.*, 2008; Necas *et al.*, 2000; Duval *et al.*, 1999; Whitehair *et al.*, 1993). Other breeds commonly reported as high risk are the Saint Bernard, Labrador retriever, chow chow, boxer, Yorkshire terrier, Newfoundland, American Staffordshire terrier, English bulldog, and German short-haired pointer (Wiles *et al.*, 2017; Taylor-Brown *et al.*, 2015; Adams *et al.*, 2011; Witsberger *et al.*, 2008; Necas *et al.*, 2000; Duval *et al.*, 1999; Whitehair *et al.*, 1993). Breeds reported to be at low risk of CCLD include the German shepherd dog, cocker spaniel, Lhasa apso, Siberian husky, Scottish terrier, Boston terrier, Weimaraner, miniature and standard dachshund, and mixed breeds (Boge *et al.*, 2019; Wiles *et al.*, 2017; Taylor-Brown *et al.*, 2015; Witsberger *et al.*, 2008; Necas *et al.*, 2000; Duval *et al.*, 1999; Whitehair *et al.*, 1993). Some breeds, such as the golden retriever, are reported as high risk in some studies and low risk in others (Wiles *et al.*, 2017; Taylor-Brown *et al.*, 2015; Witsberger *et al.*, 2008; Whitehair *et al.*, 1993).

Figure 3. Rottweiler, a breed reported to be at high risk of cranial cruciate ligament disease. Photo: Lisa Gustafsson.

Body weight and body condition score

Body weight is a commonly discussed risk factor for CCLD, and increasing body weight has been associated with greater risk of disease (Taylor-Brown *et al.*, 2015; Duval *et al.*, 1999; Whitehair *et al.*, 1993). The mean and median body weights for dogs affected by CCLD typically vary from 24.2 to 35.4 kg (Boge *et al.*, 2019; Taylor-Brown *et al.*, 2015; Necas *et al.*, 2000; Duval *et al.*, 1999). In human medicine, high body mass index (a value derived from body weight and height to broadly classify people into weight categories) is described as a risk factor for non-contact anterior cruciate ligament injury (Evans *et al.*, 2012; Uhorchak *et al.*, 2003). The association between body condition score, body weight within breed, and CCLD in dogs has been evaluated. Taylor-Brown *et al.* (2015) reported that dogs with high body weight within their breed had 3.4 times the odds of diagnosis compared to dogs with low body weight within their breed. Furthermore, Santarossa *et al.* (2020) reported that dogs with CCLD had higher body condition scores, higher body fat percentages and lower muscle condition scores than a control population. Whether the increased body condition scores and fat percentages, as well as the lower muscle condition scores, are risk factors for CCLD or simply a consequence of decreased activity secondary to the clinical manifestations of CCLD is not known.

Sex

Research results on the association between sex, neuter status, and CCLD conflict. Some studies report that neutered dogs have a higher risk of CCLD (Taylor-Brown *et al.*, 2015; Witsberger *et al.*, 2008; Duval *et al.*, 1999), while another found increased odds for female dogs (Adams *et al.*, 2011).

Insurance

Taylor-Brown *et al.* (2015) reported that insured dogs had four times the odds of a CCLD diagnosis compared to uninsured dogs, among dogs attending primary-care veterinary practices in England. In addition, referral was more frequent in insured dogs.

1.2.4 Aetiology

The exact aetiology of CCLD remains unknown, but genetic, immune-mediated, infectious, metabolic, hormonal, developmental, and primary matrix and/or cell abnormalities have been suggested to contribute to the disease development (Hayashi, 2018; Cook, 2010).

Several studies have evaluated the effect of conformational factors on the development of CCLD. One such factor is the slope of the proximal joint surface of tibia, whose association with CCLD has been studied thoroughly (Healey *et al.*, 2019; Buote *et al.*, 2009; Inauen *et al.*, 2009; Cabrera *et al.*, 2008; Reif & Probst, 2003). Some theories suggest that a steeper tibial plateau increases the risk of CCLD. Differences in the shape of the proximal tibia have been documented, but whether these affect the pathogenesis of CCLD is unclear (Wilke *et al.*, 2002). A recent study by Kyllar and Cizek (2018) reported a strong correlation between degenerative changes in CCLs and increasing tibial plateau slopes in dogs without clinical signs of CCLD. This supports the theory that a steeper tibial plateau slope increases the shear forces of the ligament, which can predispose to CCLD.

The distal femoral intercondylar notch can be narrowed in dogs and humans with CCLD/anterior cruciate ligament injury, due to osteophyte formation. This narrowing is suggested to impinge upon the CCL, altering the composition of the ligament and resulting in subsequent ligament laxity (Comerford *et al.*, 2006). Aiken *et al.* (1995), comparing the intercondylar notch in normal stifles and those affected by CCLD, found narrower intercondylar notches in stifles with CCLD. Whether CCLD is a result of a narrow intercondylar notch or a narrow intercondylar notch is a result of CCLD with secondary OA changes has yet to be determined. However, Kyllar and Cizek (2018) described a pattern of increasing structural changes in the CCLs and narrowing intercondylar notches in dogs with no clinical signs of CCLD. This supports the theory that a narrow intercondylar notch increases compression of the ligament, which could predispose to ligament rupture.

The fact that some breeds are predisposed to CCLD suggests a genetic component in the disease aetiology. Heritability of CCLD has been estimated at 0.27 in the Newfoundland and 0.55–0.886 in the Labrador retriever, suggesting that 27% to 88.6% of the phenotypic expression of CCLD is due to genetics, and the rest to environmental factors (Cook *et al.*, 2020; Wilke *et al.*, 2006). Several studies have investigated the genetic basis of CCLD, and specific chromosomal regions have been associated with CCLD (Lauren *et al.*, 2018; Lauren *et al.*, 2017; Baird *et al.*, 2014a; Baird *et al.*, 2014b). It is unclear whether genetic factors influence the structural properties of the

CCL directly or indirectly through affecting conformation factors that increase the risk of CCLD (Griffon, 2010).

1.2.5 Treatment

Surgical treatment

Over 60 variations of surgical techniques have been used to treat a ruptured CCL (Bergh *et al.*, 2014). The general aim is to stabilize the stifle joint, which can be achieved in different ways. The surgical techniques are usually categorized as: extracapsular stabilization techniques, osteotomy techniques (such as tibial plateau levelling osteotomy [TPLO] and tibial tuberosity advancement [TTA]) and intra-articular recontructive techniques. The intra-articular recontructive techniques were commonly used 20–30 years ago, and involve replacement of the ruptured ligament by either an autograft (such as a portion of the patellar tendon or a strip of the fascia lata), an allograft (such as a patellar tendon from a donor), or a prosthetic ligament (Conzemius & Biskup, 2018). However, these techniques are less used today since the extracapsular and osteotomy techniques have developed and are reported to have better outcomes (Conzemius & Biskup, 2018).

The surgical techniques for treating CCL rupture differ not only in concept, but also in invasiveness, degree of difficulty, necessary equipment, and associated costs. Factors that influence the veterinary treatment recommendation include patient size, age, body weight, activity level, concomitant PL, tibial plateau angle, tibial morphology, the severity and duration of lameness, and the degree of stifle joint instability (Duerr *et al.*, 2014; Comerford *et al.*, 2013). The status of the menisci and the degree of cruciate ligament rupture are often considered less important when surgeons choose a surgical technique (Duerr *et al.*, 2014). It has also been shown that the choice of treatment is influenced by the dog's insurance status. Taylor-Brown *et al.* (2015) reported that insured dogs are more likely to be surgically treated than uninsured dogs, and osteotomy procedures are performed more often in insured dogs. Due to the high number of available surgical techniques for treating CCL rupture, only those relevant to this thesis will be described below (Figure 4).

The TPLO technique was initially described by Slocum and Slocum (1993). Its aim is to control the cranial tibial thrust in a stifle joint with CCL rupture by levelling the tibial plateau, which increases the effectiveness of the stifle flexors' active force. A cylindrical cut is created in the caudal proximal tibia and the loose fragment is rotated until the desired level of the tibial plateau is achieved. The parts of the osteotomy are stabilized with a TPLO plate (Figure 4; Slocum & Slocum, 1993). Tibial plateau levelling osteotomy was the preferred technique for treating CCL rupture in medium, large, and giant dogs by members of the Veterinary Orthopaedic Society in the US in 2016 (Von Pfeil *et al.*, 2018). Financial concerns and the perceived risk of complications were the most common reasons for not choosing TPLO (Von Pfeil *et al.*, 2018).

The TTA technique was introduced by Montavon *et al.* (2002). Its aim is to reduce the cranial tibial thrust by advancing the tibial tuberosity so that the patellar ligament is perpendicular to the tibial plateau. A transverse osteotomy of the tibial tuberosity is performed, the tibial tuberosity is advanced, and a plate and a cage are used to stabilize the osteotomy (Figure 4). In the study of preferred method for surgical treatment of CCL rupture in medium, large, and giant breeds, only 13.9% of the veterinarians preferred TTA (Von Pfeil *et al.*, 2018). The perceived risks of complications and secondary meniscal tears were the most common reasons for not choosing TTA (Von Pfeil *et al.*, 2018). The modified Maquet procedure (MMP) is a variation of the TTA procedure. However, the distal part of the osteotomy segment is still attached to tibia, which is not the case in the TTA procedure (Ness, 2016; Etchepareborde *et al.*, 2011). Different techniques for stabilizing the osteotomy segment during MMP have been described. In one of the more recent, a titanium foam wedge is placed in the osteotomy gap and secured by a pin and a tension band wire (Ness, 2016). The MMP is not among the techniques most commonly preferred by veterinarians for treating CCL rupture (Duerr *et al.*, 2014)

Extracapsular stabilization techniques aim for stifle joint stabilization by placing extracapsular sutures. A variety of suture origins and insertions have been described (Schulz, 2013). A common extracapsular stabilization technique is the lateral fabellotibial suture (LFS), where a suture is passed around the lateral fabella and through a drilled hole in the proximal tibial tuberosity and secured by a crimp (Schulz, 2013). The LFS procedure was preferred by 5.9% of the veterinarians in the study on treating CCL rupture in medium, large, and giant breeds (Von Pfeil *et al.*, 2018). The most common reasons for not choosing LFS were the risk of implant failure and the perceived risk of unsatisfactory outcome (Von Pfeil *et al.*, 2018).

However, extracapsular stabilization was the most commonly recommended treatment for small dogs among ACVS diplomates and primary care veterinarians in the US (Duerr *et al.*, 2014). Thus, it seems that the patient's size plays a major role in whether the LFS procedure is recommended.

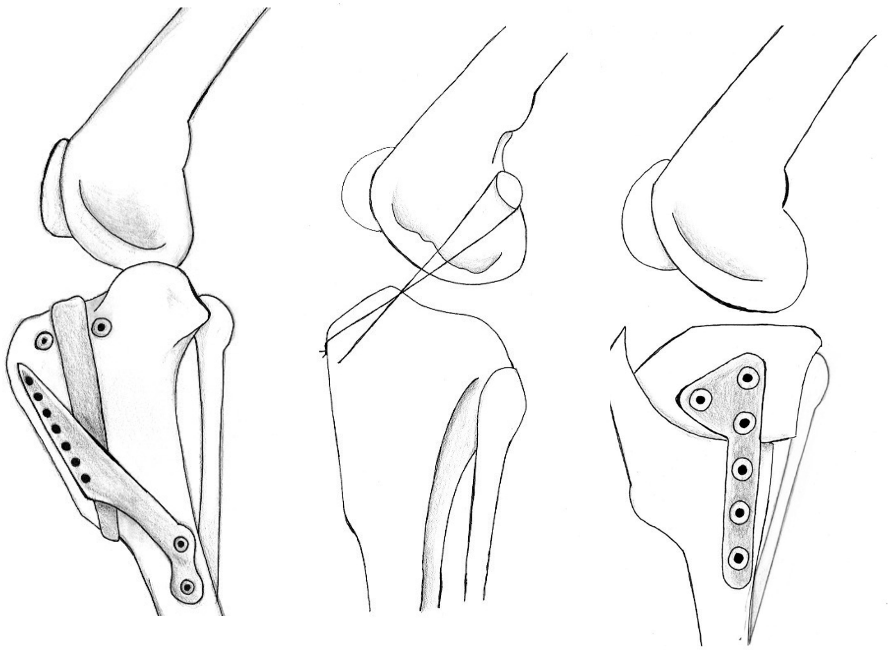


Figure 4. Overview of commonly used surgical techniques for treating cranial cruciate ligament disease. Left: tibial tuberosity advancement; Centre: lateral fabellotibial suture; Right: tibial plateau levelling osteotomy. Illustrations: Johan Bergdahl

Arthrotomy or arthroscopy is commonly performed in dogs with CCLD to evaluate the degree of cruciate ligament rupture (which may be partial or complete), the severity of OA, and concurrent meniscal damage. In an ex vivo study, arthroscopy with meniscal probing was reported to have the highest sensitivity and specificity for detecting meniscal damage (Pozzi *et al.*, 2008). The majority of meniscal injuries are treated via resection or release, and the goal of the treatment is to decrease pain and maintain meniscal function (Franklin *et al.*, 2018; Pozzi & Cook, 2018). Meniscal resection includes removing all damaged meniscal tissue, being careful not to cause iatrogenic damage to other joint structures, while preserving as much of the intact meniscus as possible (Franklin *et al.*, 2018). Meniscal release is performed to lower the risk of subsequent meniscal injury by transecting the medial meniscus or the caudal meniscotibial ligament. The goal of this release is to prevent impinging on the meniscus between the tibial and femoral condyles (Pozzi & Cook, 2018). Meniscal release has significant effects on both meniscal biomechanics and biology since it disrupts the organization of the collagen fibres in the meniscus (Pozzi & Cook, 2018). Collagen organization is important in meniscal function, and its disruption reduces meniscal stabilizing properties and increases meniscal collapse during weight bearing (Pozzi & Cook, 2018). It has been suggested that the pros and cons of meniscal release should be thoroughly evaluated in every single case because of its large effect on meniscal biomechanics and biology (Franklin *et al.*, 2018; Pozzi & Cook, 2018). Sufficient evidence is not available to support one surgical intervention over another, according to a review that evaluated both meniscal resection and release (McCready & Ness, 2016b).

Conservative treatment

Conservative treatment, also referred to as nonsurgical treatment, often involves a combination of restricted activity, physiotherapy, pain-modulating therapy, and, if indicated, weight loss (Comerford *et al.*, 2013). Dietary supplements such as glucosamine/chondroitin sulphate and omega-3 are also commonly recommended parts of conservative treatment (Duerr *et al.*, 2014). Conservative treatment is widely used in dogs under 15 kg (Comerford *et al.*, 2013). However, evidence regarding the outcome of conservative treatment is scarce.

Rehabilitation

Rehabilitation after orthopaedic surgery, aimed to restore function, balance, coordination, and strength, has become increasingly common in dogs (Baltzer, 2020). The rehabilitation protocol usually involves cryotherapy and passive range of motion exercises during the first days after surgery, while the following period may include aquatic therapy such as water treadmill, therapeutic exercises, and increasing activity to restore normal gait pattern and function (Baltzer, 2020).

1.2.6 Surgical complications

Surgical complications can prolong the healing process, cause greater postoperative pain, and result in additional costs for the animal owner (Nicoll *et al.*, 2014). The surgical techniques for treating CCL rupture are associated with a variety of complications that can be divided into pre-, intra- and post-operative, depending on the time of onset. Complications in dogs surgically treated for CCL rupture have been thoroughly evaluated, and several risk factors such as the dog's age, body weight, and breed; the experience of the surgeon; and the use of postoperative antibiotics have been studied (Lopez *et al.*, 2018; Hans *et al.*, 2017; Yap *et al.*, 2015; Coletti *et al.*, 2014; Garnett & Daye, 2014; Christopher *et al.*, 2013; Gordon-Evans *et al.*, 2013; Wolf *et al.*, 2012; Steinberg *et al.*, 2011; Taylor *et al.*, 2011; Fitzpatrick & Solano, 2010; Casale & McCarthy, 2009; Tuttle & Manley, 2009; Pacchiana *et al.*, 2003).

Some complications such as surgical site infection (SSI), subsequent meniscal injury, and swelling or bruising of the surgical wound can occur after surgical treatment of a CCL rupture regardless of the surgical technique, while others are procedure specific (Clark *et al.*, 2020; Cox *et al.*, 2020; Brown *et al.*, 2016; Yap *et al.*, 2015; Dymond *et al.*, 2010; Casale & McCarthy, 2009; Pacchiana *et al.*, 2003). Complications associated with TPLO surgery include tibial tuberosity and fibular fractures, implant failure, and patellar tendon desmitis, and the overall complication frequency ranges from 11.4% to 36% (Coletti *et al.*, 2014; Garnett & Daye, 2014; Fitzpatrick & Solano, 2010; Bergh *et al.*, 2008; Stauffer *et al.*, 2006). The frequency of complications after LFS surgery, including problems associated with the suture material used for joint stabilization, is not as commonly evaluated, but one study reported a frequency of 17.4% (Casale & McCarthy, 2009). Reported complications after TTA include tibial tuberosity fracture, implant failure, and medial PL, and frequencies range from 19% to 31.5% (Nutt *et al.*, 2015; Hirshenson *et al.*, 2012; Wolf *et al.*, 2012; Lafaver *et al.*, 2007).

Direct between-studies comparisons of complication severity and frequency can be challenging due to differences in complication classification and study design. A set of standardized definitions of complications, with criteria for reporting, has been proposed in order to facilitate such comparisons (Cook *et al.*, 2010). The complications are classified according to their time of onset (perioperative, short-term, mid-term, and long-term) and severity (catastrophic, major, and minor).

1.2.7 Long-term outcome and prognosis

There is no consensus on which surgical technique yields the best result in dogs with CCLD (Bergh *et al.*, 2014). The most studied surgical procedures are TPLO followed by LFS and TTA, and only a limited number of studies compare outcomes for more than two surgical techniques (Pinna *et al.*, 2020; Krotscheck *et al.*, 2016; Bergh *et al.*, 2014; Mölsä *et al.*, 2014; Christopher *et al.*, 2013; Mölsä *et al.*, 2013; Conzemius *et al.*, 2005; Moore & Read, 1995). A variety of methods are used to assess treatment outcomes including owner questionnaires, orthopaedic evaluation, gait analysis, and diagnostic imaging.

The long-term outcome after surgical treatment of CCL rupture is generally reported as good or successful (Livet *et al.*, 2019; Christopher *et al.*, 2013; Au *et al.*, 2010; Dymond *et al.*, 2010). Current evidence supports TPLO as the technique best able to return dogs to full function, with better functional recovery in the intermediate postoperative period after TPLO than after LFS (Bergh *et al.*, 2014). Only a few studies have evaluated outcome of treating CCLD conservatively (Wucherer *et al.*, 2013; Chauvet *et al.*, 1996; Vasseur, 1984; Pond & Campbell, 1972). Wucherer *et al.* (2013) compared surgical treatment with TPLO and conservative treatment (physical therapy, weight loss and NSAID treatment) in overweight dogs with a body weight over 20 kg. The surgically treated dogs had better outcomes than those treated conservatively, but almost two thirds of the conservatively treated dogs that participated in the one year follow-up had a successful outcome.

Treatment outcome is optimally assessed in blinded, randomized, and controlled clinical trials. However, the number of such trials reporting follow-up of surgical treatment of CCLD is very low. It is important that the follow-up period is long enough to evaluate long-term effects on joint biomechanics and biology, but many studies evaluating outcomes in dogs with CCLD have follow-up periods of under six months (Bergh *et al.*, 2014). Loss to follow-up is another common problem. Reasons for exclusion from, or loss to, follow-up examinations vary between studies and include death/euthanasia, postoperative complications, contralateral CCLD, other orthopaedic comorbidities, or owners who are unwilling to participate or cannot be contacted (Moore *et al.*, 2020; Mölsä *et al.*, 2014; Christopher *et al.*, 2013; Gordon-Evans *et al.*, 2013; Moeller *et al.*, 2010). In some studies, the loss to follow-up is substantial; the number of dogs that participate in the follow-up may be less than 50% of those enrolled in the study (Moore *et al.*, 2020; Krotscheck *et al.*, 2016; Mölsä *et al.*, 2014; Christopher *et al.*, 2013; Nelson *et al.*, 2013; Au *et al.*, 2010; Moeller *et al.*, 2010). This increases the risk of bias in the outcome assessment, since dogs lost to follow-up may differ from the dogs that complete the study (Dohoo *et al.*, 2009). In the worst case scenario, all dogs lost to follow-up were euthanized due to unsuccessful outcome. There is no simple way of dealing with this problem. However, survival analysis is an appropriate method for analysing results from studies suffering loss to follow-up, since the study participants can contribute information as long as they are observed. The survival analysis should, if possible, be complemented with information about the reason for loss to follow-up. Survival analysis, used in human orthopaedic studies, has also been used in some canine studies (Khan, 2017; van Rijn *et al.*, 2015; Muir *et al.*, 2011).

Although long-term results of treatment for CCLD are generally reported as successful, the disease frequently results in progressed OA and chronic pain (Livet *et al.*, 2019; Christopher *et al.*, 2013; Mölsä *et al.*, 2013; Au *et al.*, 2010). Mölsä et al. (2013) evaluated the long-term outcomes and prevalence of chronic pain after CCL surgery in dogs treated with osteotomy techniques or extracapsular or intracapsular stabilization procedures. The evaluation included a questionnaire asking owners to assess their dog's chronic orthopaedic pain on the Helsinki chronic pain index and to give their opinion of the surgical outcome. The mean follow-up time was 2.7 years, and 253 questionnaires were completed. The owners considered the surgical outcome excellent in 54%, good in 42.9%, and poor in 3.1% of the dogs. According to the owners, 22.3% of the dogs showed lameness sometimes, often, or always, and almost one third (31.1%) had results that indicated chronic pain on the Helsinki chronic pain index. Christopher *et al.* (2013) assessed long-term outcomes after TPLO, TTA, and TightRope extracapsular stabilization and reported that, based owners' assessments on a visual analogue scale, around 50% of the dogs still showed some pain more than a year after the surgical procedure. Altogether, these results indicate that no technique consistently results in long-term pain-free outcomes. Whether and how often chronic pain and lameness result in euthanasia in dogs with CCLD, and whether the treatment method is associated with the risk of euthanasia, is not known. Nor is it known whether and to what extent dog owners choose euthanasia instead of treatment when their dog is diagnosed with CCLD or whether factors such as the dog's age, body weight, and concurrent diseases are associated with increased risk of euthanasia.

1.3 Data sources for companion animal research

Population-level data are required to estimate population measures of disease incidence or prevalence. Such data can be either primary, i.e., collected for the purpose of the study, or secondary, i.e., collected for another purpose (Sørensen *et al.*, 1996). An advantage of using secondary data is that the information already exists, which reduces the time and expense of its collection (Sørensen *et al.*, 1996). Disadvantages of using secondary data include potential problems with validation and quality (Sørensen *et al.*, 1996). In addition, the selection during the original collection is not under the control of the researcher (Sørensen *et al.*, 1996). Thus, the data may lack information that would have been of interest for the research project. Factors that can affect the quality of secondary data are the accuracy, completeness, size, format, availability, and registration period of the data (Sørensen *et al.*, 1996). Sources of secondary data in companion animal research include records from animal hospitals/clinics and insurance data (Egenvall *et al.*, 2009).

1.3.1 Insurance data

A great advantage of using insurance data is the inclusion of information not only about disease cases, but also about the background population, i.e., animals that were insured but never presented to a veterinarian. Insurance data are suitable for calculating population-based estimates of disease occurrence, if a sufficient portion of the dog population is insured. In Sweden, approximately 90% of the dog population was insured during 2017, which is the highest such insurance coverage worldwide (Agria Pet Insurance, 2017). Agria Pet Insurance, the largest pet insurance company in Sweden, covered around 38% of the Swedish dog population in 2016 (P. Olsson, 2020, personal communication[1]). The Agria database has been used in many companion animal research projects on diseases such as epilepsy, adrenocortical insufficiency, and dystocia, and it was validated against practice records over 20 years ago (Hanson *et al.*, 2016; Heske *et al.*, 2014;

[1]Patrik Olsson, Agria Pet Insurance, 2020-03-30

Bergström *et al.*, 2006; Egenvall *et al.*, 1998). Demographic data such as breed and sex in the database and practice records agreed excellently, while diagnostic information and birth dates had fair agreement.

The generalizability of results from a study conducted on insurance data to the general population may be limited as the mortality and morbidity of insured animals cannot be assumed to reflect those of the uninsured population (Egenvall *et al.*, 2009). Insurance conditions may also vary between companies and countries. Another limitation of insurance data is that only claims with associated costs reaching the policy's deductible are registered; minor events with costs lower than the deductible will not be registered. Furthermore, depending on the level of information included in the data, it may be impossible to evaluate treatment and other details of specific disease cases. Despite these limitations, insurance data are very valuable for evaluating disease occurrence in a population, especially in countries like Sweden with a high proportion of the dog population covered by insurance.

1.3.2 Medical records

Medical records often include specific details about disease cases, such as diagnostic procedures and treatment methods. Thus, these data are feasible for evaluating disease characteristics and treatment outcomes. However, the size and structure of the source population is unknown, and therefore population-based estimates such as incidence or prevalence cannot be calculated (Egenvall *et al.*, 2009). In addition, there is a risk of referral bias, i.e., a selection towards more complicated cases, if data from a referral hospital are studied (Egenvall *et al.*, 2009). Several databases in various countries compile information from the medical records of different hospitals and clinics. For example, the Veterinary Medical Database[2] includes data from several North American university hospitals, the VetCompass Programme[3] collects information from more than 1800 veterinary practices in the UK, and the Small Animal Veterinary Surveillance Network[4] (SAVSNET) collects data from more than 500 veterinary practices in the UK. No equivalent database is currently available in Sweden.

[2] https://vmdb.org/

[3] https://www.rvc.ac.uk/vetcompass

[4] https://www.liverpool.ac.uk/savsnet/

2. Aims

Stifle joint diseases including CCLD are common in dogs, but population-based estimates of disease occurrence are limited in the literature. Knowledge about mortality due to CCLD and the factors that influence survival after CCLD treatment is also lacking. The aims of this doctoral project were to investigate the epidemiology of SJD and CCLD in dogs and to evaluate the outcomes after CCLD treatment.

The specific objectives were to

- calculate population-based estimates of SJD and CCLD incidence rates (IRs) and relative risks (RRs) and to present the proportional distributions of stifle joint diagnoses within the breeds most commonly presenting with SJD;

- investigate whether, and to what extent, dogs affected by CCLD have other diseases prior to the CCLD;

- evaluate the effects of surgical technique and other risk factors on developing severe postoperative complications in dogs with CCLD; and

- estimate the effects of treatment method and other risk factors on survival in dogs with CCLD and calculate population-based estimates of the cause-specific mortality due to CCLD.

3. Materials and Methods

This section provides an overview of the methods used in the included studies. Detailed information on the materials and specific methods can be found in the papers.

3.1 Evaluation of the epidemiology (Papers I & II)

3.1.1 Data

The database for the epidemiological studies was created by extracting data from the Agria Pet Insurance database for dogs insured 2011–2016. The database included dogs covered by veterinary care insurance, life insurance, or both. The included variables were sex (neuter status excluded), breed, birth year, date the dog entered and/or left the insurance programme, age at start of the observation period or at insurance enrolment, diagnostic codes for veterinary care claims and life insurance settlements (if any), and date when the claim/life insurance settlement was registered in the database. Euthanasia and natural death were not distinguished in the database. The breed and breed group variables were generated according to classifications by the Federation Cynologique Internationale and the Swedish Kennel Club. The diagnostic codes were based on the diagnostic registry used in Sweden for many years (Egenvall *et al.*, 1998; Swedish Animal Hospital Association, 1993). Cranial and caudal CLD are not distinguished in the diagnostic registry.

The insurance company applied additional conditions for some diagnoses. For example, claims for PL and osteochondrosis were only covered in dogs enrolled in insurance prior to the age of four months. The same applied to degenerative joint disease and non-traumatic CLD, but claims for these disorders were also covered in older dogs after a waiting period of 12 months after insurance enrolment.

Owners chose the deductible limit and maximum annual reimbursement upon enrolling in the insurance plan. The total cost of all claims during rolling 125-day periods needed to exceed the deductible of the insurance for a claim to be registered in the database. There was no information about claims prior to the observation period or diseases present before or at the time of insurance enrolment. Exclusion criteria were missing or uncertain information about birth year, sex, age, or date of enrolment.

3.1.2 Epidemiological measures

Two historical cohort studies were performed to investigate the epidemiology of SJD in dogs. All dogs with SJD were included in Paper I, while Paper II included dogs with CLD. Data analysis was performed in RStudio version 1.2.1335 (RStudio, 2020). Dog-years at risk (DYAR) were based on the total duration of insurance coverage for each dog during the study period, and the DYAR for IR estimation was calculated until the first SJD/CLD claim. Cause-specific mortality due to CLD was calculated in the same manner. Bonferroni-adjustment based on the number of subgroups in the comparison was performed to adjust for multiple comparisons.

Relative risk for SJD and CLD was computed for all dogs and for subgroups divided by breed, breed group, and sex by dividing the IR of the subgroup of interest with the IR of the rest of the population. The distribution of stifle joint diagnoses within the breeds most commonly presenting with SJD was described. Previous diagnoses were evaluated in dogs with CLD to evaluate comorbidities that could potentially influence treatment decisions and outcomes in the affected dogs.

3.2 Evaluation of treatment outcomes (Papers III & IV)

3.2.1 Data

A database for evaluating treatment outcomes was generated from clinical files on dogs diagnosed with CCLD at two animal hospitals: the small animal clinics at the University Animal Hospital in Oslo, Norway (Hospital 1), and the University Animal Hospital in Uppsala (Hospital 2), Sweden, in 2011–2016. The inclusion criterion was a diagnosis of CCLD confirmed by either a cranial drawer test, a positive tibial thrust, and/or inspection of the ruptured ligament by arthroscopy or arthrotomy. Dogs diagnosed at the hospitals but referred to other hospitals for surgical treatment were excluded. Dogs with only mild fraying of the CCL (assessed during visual inspection of the ligament) were also excluded. The database included variables such as breed, age, body weight, sex (not neuter status), concurrent orthopaedic and non-orthopaedic diseases, variables related to or evaluated during surgical treatment (surgical technique, degree of cruciate ligament rupture, concurrent meniscal injury, surgical complications, surgeon experience, duration of anaesthesia, antibiotic use), and the dates of presentation, treatment initiation and subsequent CCLD (in dogs with subsequent CCLD). Date and reason for death/euthanasia were also registered (if available). Telephone interviews were performed with dog owners and referring veterinarians in case of missing information in the medical records. A standardized protocol was used for the interviews, including questions about postoperative complications, subsequent contralateral CCLD, and date and reason for euthanasia. The dogs were followed until the date of the telephone interview with the dog owner or, if the owner could not be reached, the last recorded visit in the medical record. Dogs were classified as overweight or not based on the clinician's assessment.

3.2.2 Classification of complications

The effects of the treatment method and other risk factors on severe postoperative complications were assessed in Paper III. The severity of the complications was classified according to the definition by Cook *et al.* (2010):

- catastrophic: resulting in permanent unacceptable function, death or euthanasia;
- major: requiring either medical or surgical treatment to resolve; or
- minor: requiring no treatment to resolve.

One modification was made: postoperative complications resolved by treatment with topical antibiotics or a few days on NSAIDs treatment were classified as minor rather than major. A joint category, 'severe postoperative complications', was created by combining the catastrophic and major complications. Both stifles were included as separate cases in dogs with subsequent contralateral CCLD treated at the hospitals during the study period. Three treatment groups were generated: TPLO, TTA, and LFS.

Additional exclusion criteria in Paper III were treatment with techniques other than TPLO, TTA, or LFS; fewer than 14 days of follow-up; rupture of the collateral ligaments of the stifle; missing information about the duration of lameness prior to treatment initiation; and treatment of the contralateral CCL prior to the study period.

3.2.3 Classification of reasons for euthanasia/death

The effects of treatment method and other risk factors on survival in dogs with CCLD was assessed in Paper IV. Reasons for death/euthanasia were classified retrospectively as related to CCLD or not. Cranial cruciate ligament disease–related death was defined as all deaths where lameness from the affected hindlimb was the main or contributing reason for euthanasia and classified into five subcategories: persistent lameness, subsequent contralateral CCLD, postoperative complications, guarded prognosis for return to full function, or other reasons. Deaths unrelated to CCLD were grouped according to according to Fleming *et al.* (2011) by organ system and pathophysiologic process. In dogs with subsequent contralateral CCLD treated at the hospitals, only the first stifle was included in the analysis. Three treatment groups were generated: osteotomy (including TPLO, TTA, and MMP), LFS, or conservative treatment. Additional exclusion criteria in Paper IV were missing information about duration of lameness before treatment initiation, rupture of the collateral ligaments of the stifle, euthanasia at time of diagnosis, less than 14 days follow-up time, and surgical treatment of contralateral CCLD prior to the study period.

3.2.4 Statistics

All statistical analyses were conducted in Stata 15 (StataCorp 2017; StataCorp, 2019). Appropriate parametric and non-parametric methods were used to examine group differences in the descriptive variables. Kaplan-Meier survival curves were applied to describe differences in time to event (severe postoperative complication or death) for the treatment groups. Cox proportional hazards models were used to estimate the effects of surgical technique and other risk factors on severe postoperative complications and survival. In Paper III, the outcome was a severe postoperative complication: dogs that were lost to follow-up, were euthanized/died for reasons unrelated to severe postoperative complications or had minor or no postoperative complications were censored in the analysis. In Paper IV, two Cox proportional hazards models were applied: one estimating disease-related survival and one estimating overall survival. Dogs that were alive at the end of the study period or lost to follow-up were censored in the overall survival analysis, and those that were dead or euthanized for reasons unrelated to CCLD were censored in the disease-related survival analysis. Treatment was set to the main exposure variable, and variables on the path from the treatment to the outcome (such as the use of postoperative antibiotics) were considered intervening variables and thus excluded from the analyses.

4. Results

The most important findings from Papers I–IV are reported in this section.

4.1 Evaluation of the epidemiology (Papers I & II)

The database included just over 600,000 insured dogs. Approximately 700 dogs were screen out by the exclusion criteria. Of the included dogs, 61.8% had both veterinary care insurance and life insurance, 35.5% had only veterinary care insurance, and 2.7% had only life insurance. Descriptive features of the full study population are shown in Table 1.

Table 1. Descriptive features of dogs insured by Agria Pet Insurance in Sweden, 2011–2016

	Insurance	
	Veterinary care	Life
Duration of insurance (years)	>1.7 million	>1.1 million
Sex (%)		
Female	49.1	49.5
Male	50.9	50.5
Number of dogs with SJD	9,624	784
Number of dogs with CLD	4,167	447
CLD	4,142	432
Bilateral CLD	45	15
Age at SJC claim	5.6 y (7.1 w–16.2 y)*	6.0 y (11.9 w–12.2 y)
Age at CLD claim	7.1 y (13.3 w–16.0 y)*	6.6 y (16.3 w–12.0 y)

*Age at first SJD/CLD veterinary care claim during 2011–2016

Age is reported as median (range)

SJD stifle joint disease, *CLD* cruciate ligament disease, *y* years, *w* weeks

The IR of SJD was 55.4 (95% CI: 54.3–56.5) cases per 10,000 DYAR. The diagnostic registry included 222 stifle joint diagnoses grouped into 14 diagnostic categories. Of the dogs with SJD claims, 43.5% had a claim for CLD, 29.8% for PL, 21.2% for pain or unspecific signs from the stifle, 11.6% for degenerative changes, and 6.85% for arthritis. Of the PLs, 88.7% were medial, 8.21% were lateral, and 3.08% were unspecified. The following diagnostic categories occurred separately in under 5% of all dogs with SJD claims: traumatic injury, meniscal injury, osteochondrosis, fracture, pain or unspecific signs (patella/fabella), tumour, other malformations and growth disorders, immune-mediated disease, and inflammatory disease (patella/fabella). The breeds that contributed most SJD cases were the mixed breed (21.4% of all SJD-cases), Labrador retriever (4.40%), Chihuahua (3.84%), German shepherd dog (3.46%), and Rottweiler (3.40%). The distribution of the diagnostic categories in the 12 breeds that contributed the most SJD cases is presented in Figure 5. The most common SJD, CLD, had an IR of 23.8 (95% CI: 23.1–24.6) cases per 10,000 DYAR. Females were at slightly higher risk than males of both SJD in general (RR 1.06, 95% CI: 1.02–1.10, $p = 0.006$) and CLD (RR 1.13, 95% CI: 1.06–1.20, $p <0.001$).

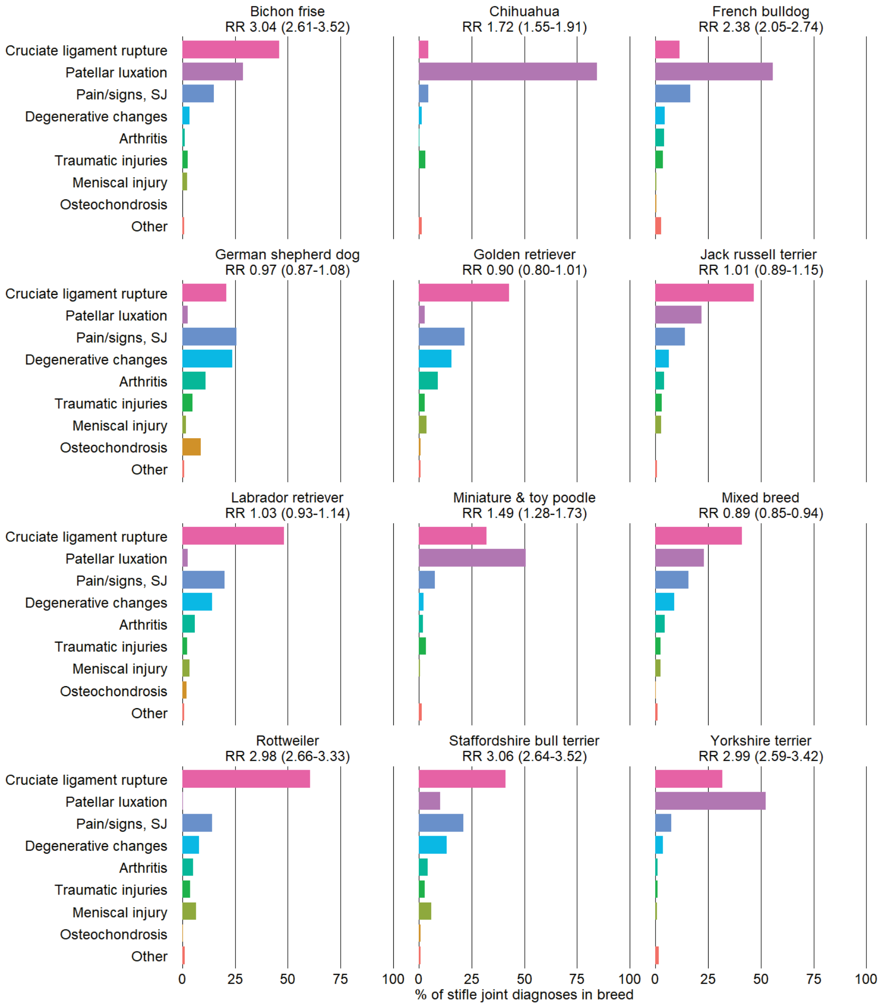


Figure 5. The relative risk of stifle joint disease and distribution of dogs within the diagnostic categories for the breeds that contributed the most cases of stifle joint disease. One dog could be included in several diagnostic categories, but only once in each category. *Pain/signs, SJ* pain or unspecific signs from the stifle joint.

The ten breeds with highest and lowest RRs for SJD and CLD (after Bonferroni correction) are presented in Figure 6.

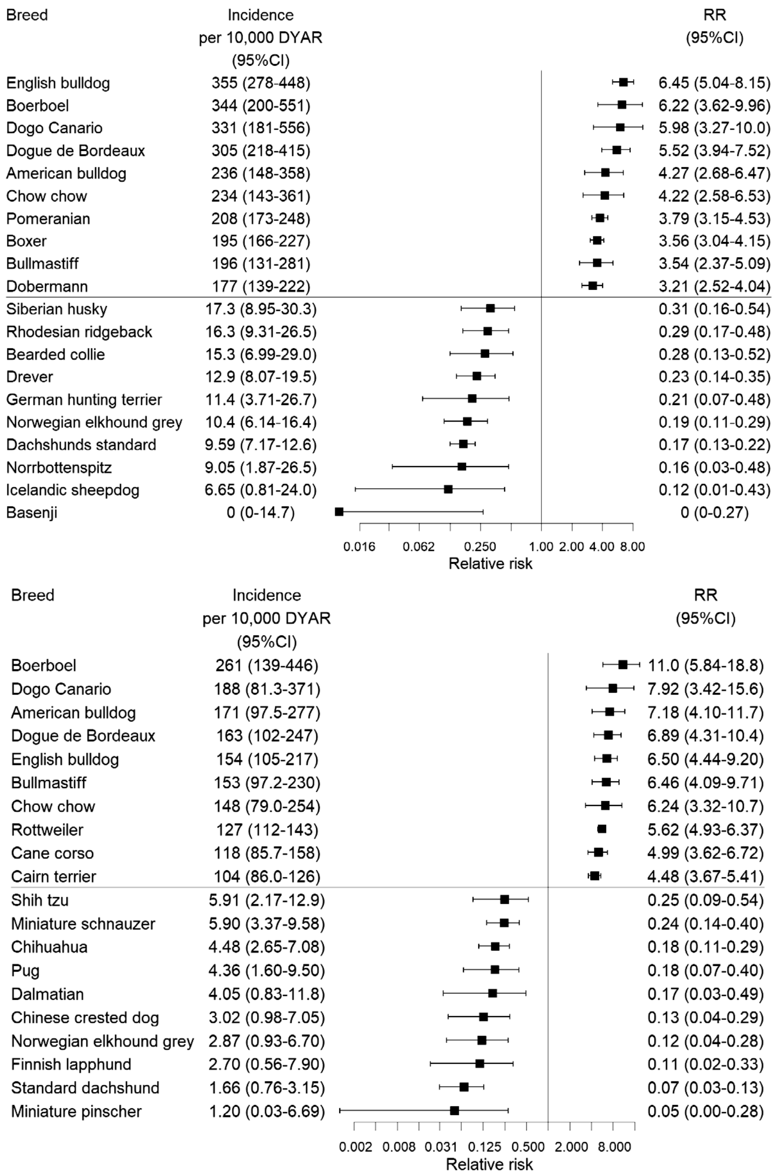


Figure 6. The ten breeds with highest and lowest relative risks for stifle joint disease (upper figure) and cruciate ligament disease (lower figure).

The age at diagnosis and at life insurance settlement due to CLD varied with breed, and the breeds with significantly higher or lower ages at those points are presented in Figure 7. In general, the breeds with significantly lower age at diagnosis and euthanasia were large and giant sized, while the breeds with significantly higher age at diagnosis were small.

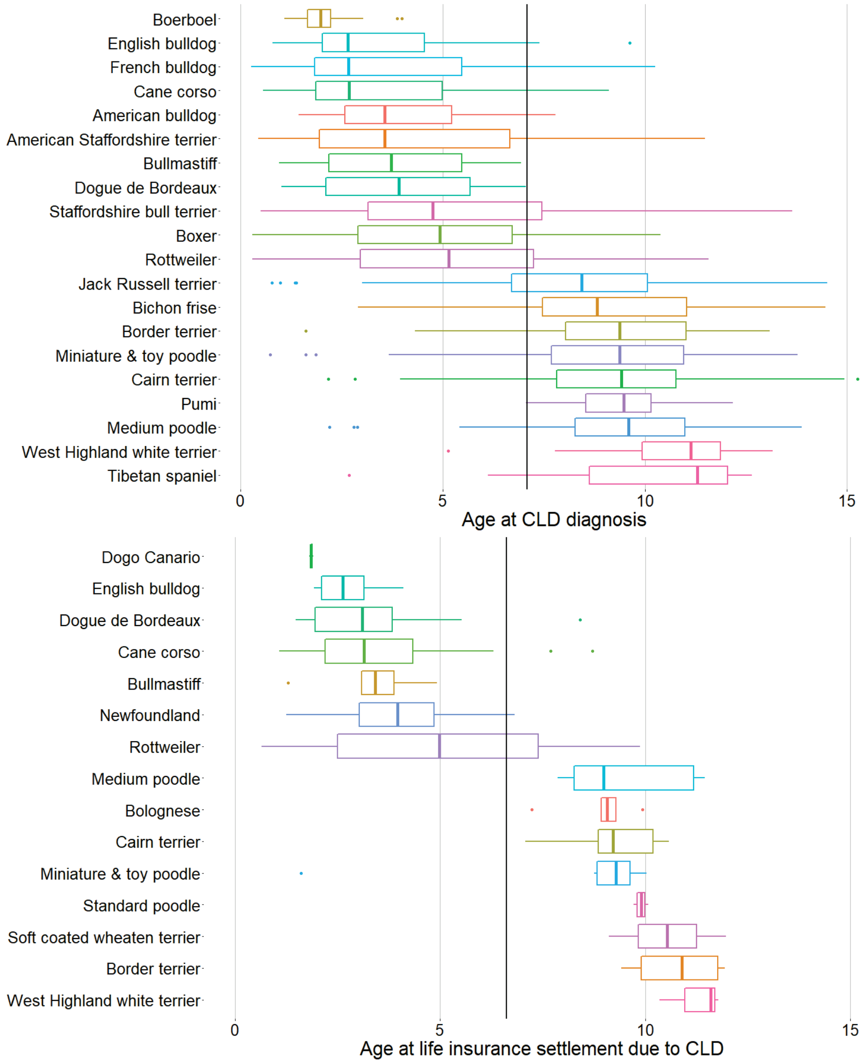


Figure 7. Age at diagnosis and at euthanasia due to cruciate ligament disease. The black lines represent the overall median age at CLD diagnosis/life insurance settlement.

Of the 4,167 dogs with veterinary care claims for CLD, 2,762 (66.3%) had concurrent life insurance. Of these, 466 (10.7%) had a life insurance settlement during the observation period, of which 234 (50.2%) were due to CLD. The median time from CLD veterinary care claim to CLD life settlement was 7 days (0–4.25 years). The cause-specific mortality rate of CLD was 4.04 (95% CI: 3.67–4.43) deaths per 10,000 DYAR. Dogue de Bordeaux (RR 30.4, 95% CI: 16.5–51.5), cane corso (RR 12.7, 95% CI: 7.04–21.2), Newfoundland (RR 9.10, 95% CI: 3.32–20.0), Rottweiler (RR 6.56, 95% CI: 4.53–9.23), boxer (RR 5.95, 95% CI: 3.30–9.93), Bernese mountain dog (RR 5.65, 95% CI: 3.20–9.28), and Labrador retriever (RR 2.09, 95% CI: 1.49–2.88) all had significantly increased risk of euthanasia due to CLD (after Bonferroni correction). The standard dachshund was the only breed with significantly decreased risk of euthanasia due to CLD (after Bonferroni correction, RR 0, 95% CI: 0–0.26)

In total, 2,656 of the 4,167 (63.7%) dogs with veterinary care claims for CLD had previous claims for other diseases. The most common reasons for previous claims were musculoskeletal disorders (37.0% of the dogs) and dermatologic conditions (26.2%). The most frequent musculoskeletal disorder was joint disease, which affected 21.9% of the dogs. Claims for SJD were most common (15.6% of the dogs), of which pain/clinical signs without confirmed cause (8.18%) and degenerative changes (3.14%) were the most common diagnoses.

4.2 Evaluation of treatment outcomes (Papers III & IV)

The database included 436 dogs with 501 affected stifles. The stifles were treated conservatively (n = 87) or surgically with TPLO (n = 84), TTA (n = 79), or LFS (n = 158). In addition, 22 stifles were treated with MMP, one stifle with arthrodesis, and one stifle with cranial wedge osteotomy. The most common non-orthopaedic comorbidities at time of CCLD diagnosis were dermatologic disease (n = 34) and endocrine disorders (n = 13). In total, 165 (37.8%) dogs had contralateral CCLD at some time point. The most common breeds were mixed-breed (n = 96), Rottweiler (n = 34), Labrador retriever (n = 27), golden retriever (n = 22), poodle (n = 22) and Jack Russell terrier (n = 16). See Table 2 for information about the descriptive features, treatment and follow-up of the dog.

Table 2. Descriptive features at time of diagnosis and data on treatment and follow-up in 436 dogs with 501 stifles affected by cranial cruciate ligament disease diagnosed at two university animal hospitals, reported at stifle level

	TPLO	TTA	LFS	Other tech*	Conservative	Euthanasia	Total
No. stifles (%)	84 (16.8)	79 (15.8)	158 (31.5)	24 (4.8)	87 (17.4)	69 (13.8)	501 (100)
Hospital (%)							
Hospital 1	8 (9.5)	79 (100)	31 (19.6)	24 (100)	28 (32.2)	7 (10.1)	177 (35.3)
Hospital 2	76 (90.5)	0 (0)	127 (80.4)	0 (0)	59 (67.8)	62 (89.9)	324 (64.7)
Body weight, kg (range)	39.6 (19–80.3)	29.2 (9.8–66.0)	12.0 (3.3–49.3)	30.3 (6.5–62.0)	19.0 (2.9–76.0)	31.0 (3.6–67.0)	25.0 (2.9–80.3)
Sex (%)							
Female	39 (46.4)	48 (60.8)	90 (57.0)	14 (58.3)	55 (63.2)	41 (59.4)	287 (57.3)
Male	45 (53.6)	31 (39.2)	68 (43.0)	10 (41.7)	32 (36.8)	28 (40.6)	214 (42.7)
Age, years (range)	5.7 (0.8–10.4)	3.9 (0.5–10.8)	7.7 (0.9–12.8)	5.7 (1.3–11.1)	7.6 (0.2–14.8)	6.4 (0.6–15.8)	6.5 (0.2–15.8)
Overweight (%)	26 (31.0)	13 (16.5)	48 (30.4)	8 (33.3)	25 (28.7)	20 (29.0)	140 (27.9)
Insurance (%)	78 (92.9)	56 (70.9)	144 (91.1)	18 (75.0)	67 (77.0)	62 (89.9)	425 (84.8)
Orthopaedic disease (%)							
Hip dysplasia	5 (5.9)	5 (6.3)	9 (5.7)	1 (4.2)	5 (5.7)	6 (8.7)	31 (3.6)
Osteochondrosis, stifle	7 (8.3)	2 (2.5)	1 (0.6)	1 (4.2)	5 (5.7)	3 (4.3)	19 (1.8)
Patellar luxation	1 (1.2)	3 (3.8)	25 (15.8)	0 (0)	8 (9.2)	3 (4.3)	40 (8.0)
Other	10 (11.9)	3 (3.8)	12 (7.6)	2 (8.3)	8 (9.2)	11 (15.9)	46 (9.2)
Non-orthopaedic disease (%)	12 (14.3)	15 (19.0)	26 (16.5)	6 (25.0)	26 (29.9)	13 (18.8)	98 (19.6)
Side (%)							
Left	48 (57.1)	43 (54.4)	79 (50.0)	12 (50.0)	40 (46.0)	33 (47.8)	255 (50.9)
Right	36 (42.9)	36 (45.6)	79 (50.0)	12 (50.0)	47 (54.0)	36 (52.2)	246 (49.1)
*Acute lameness** (%)*	52 (61.9)	55 (69.6)	120 (75.9)	12 (50)	47 (54.0)	43 (62.3)	329 (65.7)

	TPLO	**TTA**	**LFS**	**Other tech***	**Conservative**	**Euthanasia**	**Total**
Joint exploration (%)	84 (100)	44 (55.7)	146 (92.4)	5 (20.8)	8 (9.2)	5 (7.2)	292 (58.3)
Arthroscopy (%)	82 (97.6)	8 (10.1)	27 (17.1)	0 (0)	5 (5.7)	5 (7.2)	127 (25.3)
Arthrotomy (%)	18 (21.4)	36 (45.6)	128 (81.0)	5 (20.8)	3 (3.4)	2 (2.9)	192 (38.3)
*Partial CL rupture*** (%)*	14 (16.7)	14 (31.8)	28 (19.2)	1 (20)	6 (75)	4 (80)	67 (22.9)
*Caudal CL rupture*** (%)*	4 (4.8)	1 (2.3)	8 (5.5)	1 (20)	1 (12.5)	0 (0)	15 (5.1)
*Meniscal injury*** (%)*	20 (23.8)	20 (45.5)	39 (26.7)	3 (60)	2 (25)	2 (40)	86 (29.5)
Follow-up, years (range)	2.8 (0.1–7.1)	4.1 (0.0–7.4)	2.8 (0.0–7.6)	3.0 (0.0–6.7)	1.8 (0–7.5)	-	2.4 (0–7.6)
Dead at follow-up (%)	51 (60.7)	28 (35.4)	70 (44.3)	9 (37.5)	59 (67.8)	-	217 (50.2)
Cruciate-related death	14 (16.7)	10 (12.7)	22 (13.9)	4 (16.7)	25 (28.7)	-	75 (17.4)
Death due to other reason	37 (44.0)	18 (22.8)	48 (30.4)	5 (20.8)	34 (39.0)	-	142 (32.9)

*22 stifles treated with MMP, one stifle treated with stifle arthrodesis, one stifle treated with cranial wedge osteotomy

**at time of diagnosis

***% of the dogs with joint exploration

All variables are reported on stifle level. Continuous variables reported as median (range) and categorical as number (%). *TPLO* tibial plateau levelling osteotomy, *TTA* tibial tuberosity advancement, *LFS* lateral fabellotibial suture, *CL* cruciate ligament.

In total, 121 dogs (27.8%) had CCLD as the main or contributing reason for euthanasia. Euthanasia at or close to the time of diagnosis was performed in 61 dogs, of which 8 presented with bilateral disease. Euthanasia at diagnosis was more common in dogs treated at Hospital 2 (n = 55) than at Hospital 1 (n = 6, $p < 0.001$). Cranial cruciate ligament disease was the main or contributing reason for euthanasia in 60 of the 61 dogs euthanized at or close to the time of diagnosis. Of these, 23 dogs had concurrent disease that contributed to the decision of euthanasia. One dog went through surgery for brachycephalic obstructive airway syndrome before the CCLD surgery and was euthanized post-anaesthesia due to severe dyspnoea. The most common reason for euthanasia at or close to the time of diagnosis was presentation with bilateral CCLD or subsequent CCLD in dogs with previous unilateral CCLD (n = 16) or the risk that the dog would not return to full function as perceived by the owner or the veterinarian (n = 14). Several owners reported that they chose euthanasia because they believed restricted activity would be impossible during the postoperative period because the dog was highly active, or that they did not want the dog to suffer. Some owners with dogs affected by subsequent contralateral CCLD described either an unsuccessful outcome or a tough recovery period after the first CCLD treatment, and said they did not want their dog to go through that again. Previous or concurrent contralateral CCLD was more common in dogs euthanized at or close to time of diagnosis than in treated dogs (36.1% and 22.2%, respectively, $p = 0.030$). There were no significant between-group differences in sex, body weight, age at diagnosis, overweight, insurance, acute lameness, or concurrent orthopaedic or non-orthopaedic comorbidities.

In Paper III, 287 stifles in 255 dogs met the inclusion criteria, and in Paper IV, 333 dogs qualified. Figure 8 illustrates the relationship between the master database and the study populations in Papers III and IV.

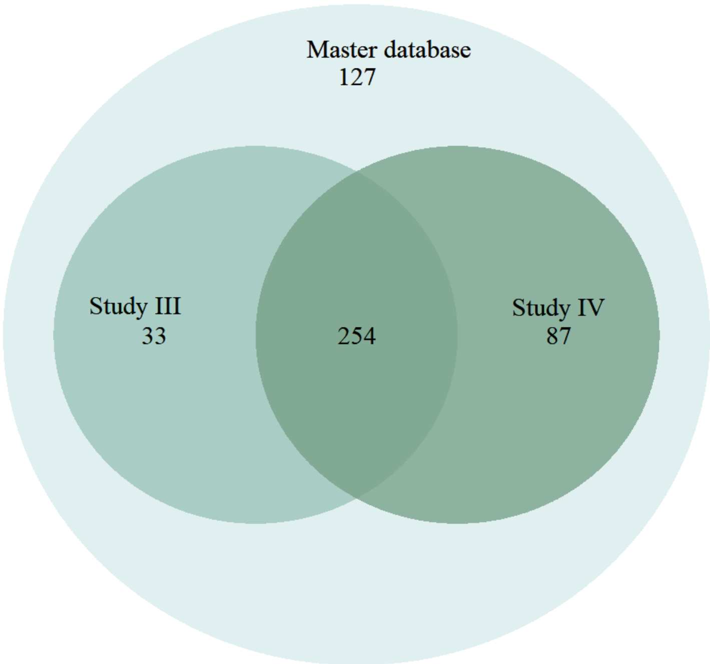


Figure 8. Overview of the number of stifles included in each paper. Paper IV included 333 dogs with 341 affected stifles since some dogs presented with bilateral disease.

Reasons for exclusion in Paper III are presented in Figure 9.

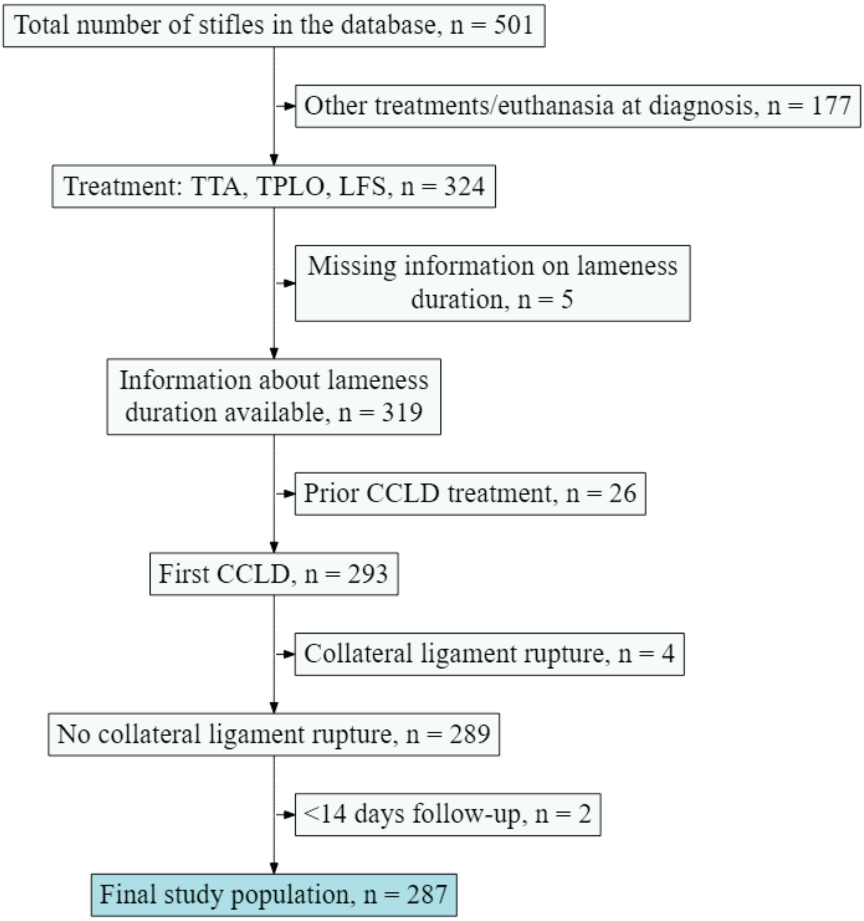


Figure 9. Flow chart of dogs excluded from the study population in Paper III.

In Paper III, 141 (49.1%) stifles were treated with LFS, 77 (26.8%) with TPLO, and 69 with TTA (24.0%). Age and body weight differed between treatment groups (median age and body weight were 7.5 years, 5.6 years, and 3.9 years/11.7 kg, 42.2 kg, and 29.0 kg for LFS, TPLO and TTA, respectively: $p < 0.001$ for both comparisons). Fourteen surgeons performed the procedures, of whom four were residents and two were board-certified. The median duration of the follow-up period was 2.3 (0–7.6) years.

In total, 72 (25.1%) stifles were affected by severe postoperative complications: 31 (22.0%) were treated with LFS, 24 (31.2%) with TPLO, and 17 (24.6%) with TTA. Of these, eight stifles were affected by catastrophic complications and the rest by major complications (according to the definitions used for classification). The most common severe postoperative complications were related to the surgical implants (n = 31), SSIs (n = 27), and subsequent meniscal injuries (n = 8). Arthrotomy or arthroscopy had been performed at the time of initial surgical treatment in all but one of the stifles affected by subsequent meniscal injury. The median time until occurrence of the first severe postoperative complication was 22 (1–768) days. Ten complications were reclassified from major to minor. These included eight cases of mild lameness that resolved with analgesic treatment and two cases of skin irritation close to the surgical wound that resolved with local antibiotic treatment. Duration of anaesthesia was only registered for 239 (83.3%) of the procedures, but varied with treatment: the median duration was 145 (45–263) minutes for the LFS procedures, 280 (125–380) minutes for the TPLO procedures, and 198 (110–320) minutes for the TTA procedures ($p < 0.001$).

Postoperative antibiotics were prescribed after 61 surgeries (21.2%): 12 (8.5%) LFS surgeries, 4 (5.2%) TPLO surgeries, and 45 (65.2%) TTA surgeries. In total, 48 (16.7%) stifles went through revision surgery due to postoperative complications: 22 (15.6%) of those treated with LFS, 15 (19.5%) treated with TPLO, and 11 (15.9%) treated with TTA.

The results of the final Cox proportional hazards model are presented in Figure 10. Age and body weight were confounders for treatment method.

Variable	Coef.	Hazard ratio 95% CI	p-value
Treatment			**0.026**
LFS	0	1.00 (-)	-
TPLO	-0.99	0.37 (0.18-0.76)	0.007
TTA	-0.57	0.56 (0.16-1.93)	0.361
Hospital			
Hospital 1	0	1.00 (-)	-
Hospital 2	0.5	1.65 (0.58-4.70)	0.345
Signalment			
Age (years)	-0.09	0.91 (0.83-1.00)	0.047
Body weight (kg)	0.05	1.05 (1.03-1.07)	<0.001

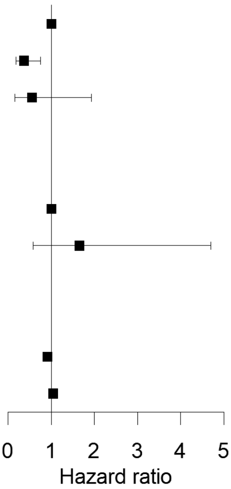


Figure 10. Results of the final Cox proportional hazards model in Paper III evaluating the effect of surgical technique and other risk factors on the hazard of severe postoperative complications. No difference was found between TTA and LFS (p = 0.361) or between TPLO and TTA (p = 0.495, Wald test). *LFS* lateral fabellotibial suture, *TPLO* tibial plateau levelling osteotomy, *TTA* tibial tuberosoty advancement, *coef* coefficient, *CI* confidence interval

Reasons for exclusion from Paper IV are presented in Figure 11.

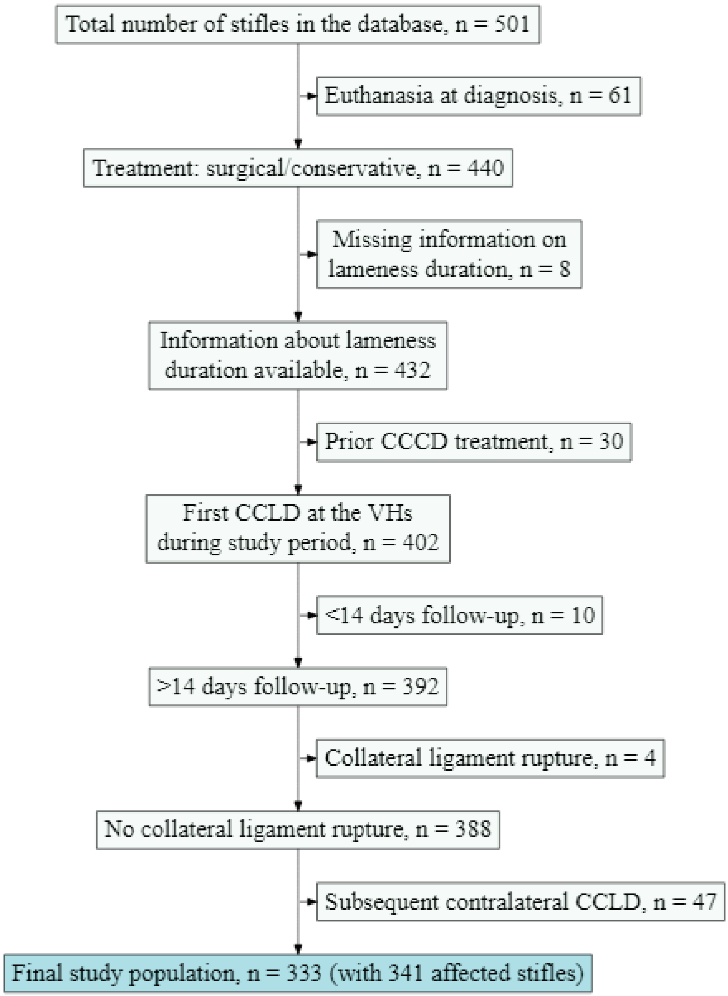
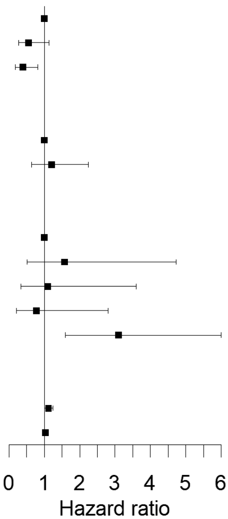


Figure 11. Flow chart of dogs excluded from the study population in Paper IV.

In Paper IV, 65 (19.5%) dogs were treated conservatively, 125 (37.5%) with LFS, and 143 (42.9%) with osteotomy procedures (71 TPLOs, 54 TTAs, and 18 MMPs). Dogs treated with osteotomy procedures were significantly younger than dogs treated conservatively or with LFS (median age 4.2 years vs. 7.6 and 7.7 years, $p < 0.001$ for both comparisons). The body weight in the osteotomy group was higher than in the other groups (median body weight 35.0 kg vs. 17.9 kg (conservative) and 11.3 kg (LFS), p <0.001 for both comparisons). The median follow-up time was 2.83 (0.04–7.61) years. At follow-up, 164/333 (49.2%) dogs were still alive, while 169/333 (50.8%) were dead/euthanized. Cranial cruciate ligament disease was the main or contributing reason for euthanasia in 61/333 dogs (18.3%). Of these, 19 were treated conservatively, 19 with LFS, and 23 with osteotomy. The most common reasons for CCLD-related euthanasia were persistent lameness (n = 25) and contralateral CCLD (n = 17). The median time to CCLD-related euthanasia was 15.6 (0.5–74) months and varied with treatment: 19.9 (2.3–45.1) months for LFS, 21.9 (0.5–68.1) months for osteotomy procedures, and 2.4 (0.6–74) months for conservative treatment.

The results of the disease-related and overall survival Cox proportional hazards models are presented in Figure 12. Age and body weight were confounders for treatment method in both models. The assumption of proportional hazards was violated for age in the overall survival model, and graphical assessment indicated that the effect of age increased on a linear scale. Thus, a time-varying effect for age was included in the final model.

Variable	Coef.	Hazard ratio 95% CI	p-value
Treatment			**0.035**
Conservative		1.00 (-)	-
LFS	-0.58	0.56 (0.28-1.14)	0.109
Osteotomy	-0.91	0.40 (0.19-0.81)	0.012
Hospital			
Hospital 1		1.00 (-)	-
Hospital 2	0.20	1.21 (0.65-2.25)	0.547
Orthopedic comorbidity			**<0.001**
None		1.00 (-)	-
Patellar luxation	0.45	1.57 (0.52-4.73)	0.420
Hip dysplasia	0.09	1.10 (0.34-3.59)	0.873
Osteochondrosis stifle	-0.24	0.78 (0.22-2.80)	0.706
Other	1.12	3.09 (1.59-6.00)	0.001
Signalment			
Age (years)	0.11	1.12 (1.01-1.25)	0.040
Body weight (kg)	0.03	1.03 (1.01-1.05)	0.001



Variable	Coef.	Hazard ratio 95% CI	p-value
Treatment			**0.002**
Conservative		1.00 (-)	-
LFS	-0.63	0.53 (0.35-0.80)	0.003
Osteotomy	-0.63	0.53 (0.35-0.81)	0.003
Hospital			
Hospital 1		1.00 (-)	-
Hospital 2	0.20	1.22 (0.85-1.77)	0.278
Non-orthopedic comorbidity	0.42	1.53 (1.05-2.22)	0.028
Signalment			
Age (years)	0.11	1.12 (1.01-1.24)	0.028
Body weight (kg)	0.03	1.03 (1.02-1.04)	<0.001
TVC (age)	0.00	1.00 (1.00-1.01)	0.006

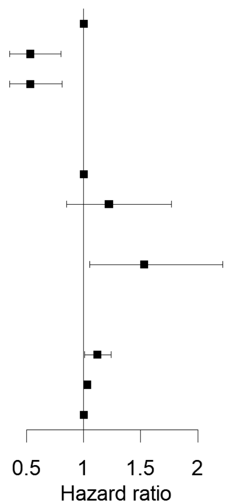


Figure 12. Results of the final Cox proportional hazards models in Paper IV evaluating the effects of treatment and other risk factors on survival in dogs with CCLD: disease-related survival (upper figure) and overall survival (lower figure). *LFS* lateral fabellotibial suture, *TVC* time varying covariate, *coef* coefficient, *CI* confidence interval

5. Discussion

5.1 Distribution of stifle joint diagnoses

In the dogs with SJD, CCLD and PL were the most common diagnoses, affecting 43.5% and 29.8%, respectively. This correlates well with the results from Johnson *et al.* (1994), who reported that CCLD and PL were the most common stifle joint diagnoses in dogs treated at 16 Veterinary Hospitals in the United States and Canada during 1980–1989.

Other common diagnoses were pain or unspecific signs from the stifle joint, degenerative changes, and arthritis. It is likely that some dogs with these diagnoses received a more specific diagnosis after further veterinary investigation. For example, 15.6% of the dogs with a CLD diagnosis had had another SJD diagnosis prior to the CLD claim, most commonly pain/clinical signs without confirmed cause and degenerative changes. It is also likely that the clinical signs in some of these dogs were caused by an underlying condition such as CLD, which had remained undiagnosed for reasons such as restricted owner economy or comorbidities that prevented anaesthesia.

The distribution of SJD diagnoses was evaluated in the twelve breeds contributing the most SJD cases. Cruciate ligament disease was among the top three diagnostic categories in all these breeds and the most common in seven breeds of various sizes (Rottweiler, Labrador retriever, Jack Russell terrier, bichon frise, golden retriever, mixed breed, and Staffordshire bull terrier). Pain or unspecific signs from the stifle joint were also relatively common in these breeds. Cranial cruciate ligament disease has been described as an organ failure of the stifle joint associated with degenerative joint disease and clinical signs such as pain and lameness (Muir, 2018;

Comerford *et al.*, 2011; Au *et al.*, 2010; Cook, 2010; Lazar *et al.*, 2005). Thus, it is probable that many of the dogs with claims for CLD, unspecific signs from the stifle joint, degenerative joint disease and/or arthritis had the same underlying pathology: an organ failure of the stifle joint. The background of this organ failure is, as mentioned in the introduction, still unknown.

Patellar luxation was among the top two diagnostic categories in all small breeds that contributed the most SJD cases (Jack Russell terrier, bichon frise, Chihuahua, Yorkshire terrier, and miniature and toy poodle), but not among the top five diagnostic categories in the large breeds (golden retriever, Labrador retriever, German shepherd dog, Rottweiler). Based on these results, it seems that PL primarily affects small breeds, and while CLD affects breeds of all sizes, it is found mainly in large and giant breeds. This is in line with previous research, and may represent true differences in breed- and size-specific disease patterns, although there may also be a bias in the veterinarians' tendency to give certain diagnoses to specific breeds or types of dog (Perry & Dejardin, 2021; O'Neill *et al.*, 2016; Taylor-Brown *et al.*, 2015; Witsberger *et al.*, 2008; Whitehair *et al.*, 1993; Priester, 1972).

5.2 Risk factors for stifle joint disease and cruciate ligament disease

5.2.1 Breed

The American bulldog, boerboel, Presa Canario, dogue de Bordeaux, and English bulldog had the highest risks of both SJD and CLD, although their rank order differed slightly on the two lists. Overall, the same breeds were at highest risk of SJD and CLD, although the Lancashire heeler, pumi, Newfoundland, American cocker spaniel, border terrier, medium poodle, and Labrador retriever were at high risk of CLD, but not SJD in general. On the other hand, the Pomeranian, Boston terrier, Prazsky krysarik, French bulldog, Chihuahua, and miniature and toy poodle breeds had a high risk of SJD, but not CLD (the full lists of breeds at high risk of SJD and CLD are shown in Papers I & II). That these breeds were mainly affected by SJD diagnoses other than CLD is supported by the results in Figure 5, showing that PL was the most common diagnosis in the Chihuahua, French bulldog, and miniature and toy poodle.

Only seven of the twelve breeds that contributed the most SJD cases were at high risk of SJD, while one, the mixed breed, actually had a lower risk than most. This may be because mixed breeds were very common in the study population and therefore contributed many of the SJD cases, despite their lower risk. On the other hand, less common breeds such as the boerboel and dogue de Bordeaux contributed with very few cases to the total case load, but had high IR of SJD due to the high number of affected dogs in proportion to the DYAR within the breeds. This stresses the importance of reporting epidemiologic measures such as IR and RR, not only the breeds with high number of disease cases, when assessing risk of disease.

Most breeds at high risk of CLD were large or giant sized, although some small and medium sized breeds were also among those at high risk. Large and giant sized breeds were especially overrepresented among the top ten high-risk breeds, and all breeds in that top ten except the chow chow and Cairn terrier were molosser types. Large breeds were not only common among high-risk breeds, but also among those at low risk of CLD, including the Rhodesian ridgeback, the German shepherd dog and the Dalmatian. The German shepherd dog is reported to be at low risk of CLD in several studies (Witsberger *et al.*, 2008; Necas *et al.*, 2000; Duval *et al.*, 1999; Whitehair *et al.*, 1993). It is not known why some large breeds are at high risk of CLD while others are at low risk. This implies, however, that factors other than breed size contribute to CLD development. Body constitution might be an important difference, as many of the molosser breeds are stocky and robust, while the large breeds at low risk (Rhodesian ridgeback, Dalmatian, German shepherd dog) have slimmer body constitution. Breed differences in CCL structure, function, and resistance to damage might also contribute. Wingfield *et al.* (2000) reported that the CCLs of Rottweilers were more vulnerable to damage than those of greyhounds, a breed reported to be at low risk of CCL in other studies (Witsberger *et al.*, 2008; Whitehair *et al.*, 1993).

That many breeds of a specific type were at high risk of CLD supports the theory of a genetic component in the disease aetiology. Moderate heritability of CCLD has been shown in the Newfoundland, a molosser-type breed included among those high risk of CLD, and several chromosomal regions have been significantly associated with the CCLD trait (Wilke *et al.*, 2009; Wilke *et al.*, 2006). The cause of the increased risk of CLD in the molosser types is unknown. Breeding reforms may be warranted to lower the IR of CLD within these breeds in the future, but the cause of the increased

CLD risk has to be confirmed in order evaluate whether and which type of reforms can be implemented.

Figure 13. Cane corso, a molosser type breed, was one of the breeds at higher risk of cruciate ligament disease. Photo: Maria Östman

5.2.2 Sex

In line with previous research, females had higher risks of both SJD and CLD than males, although the reason for their increased risks is unknown (Perry & Dejardin, 2021; Adams *et al.*, 2011; Whitehair *et al.*, 1993). Hormonal influence has been discussed as a potential contributor, but there are no conclusive studies on the effect of hormonal status or gender on the risk of CCLD (Baker & Muir, 2018; Comerford et al., 2011). Females have also been reported to have a higher risk of PL than males, although the results from different studies are inconclusive, and other studies report that males are at higher risk (Perry & Dejardin, 2021).

Neuter status is commonly evaluated as a risk factor for SJD, with studies showing that neutered dogs have increased risks of CLD, OA, and PL, but the underlying mechanism is still not fully confirmed (Anderson *et al.*, 2018; O'Neill *et al.*, 2016; Taylor-Brown *et al.*, 2015; Witsberger *et al.*, 2008; Duval *et al.*, 1999). Weight gain has been suggested as the cause of increased risk of CCLD in neutered animals, either through increased mechanical load on the stifle or through an endocrine pathway that releases pro-inflammatory adipokines from the adipose tissue that may contribute to chronic inflammation and degeneration in the stifle joint (Baker & Muir, 2018; Comerford et al., 2011; Whitehair et al., 1993). The effect of neutering could not be evaluated in Papers I and II due to lack of information in the insurance database. In a 1998 Swedish survey, only 7.2% of the females and 3.7% of the males were neutered (Egenvall et al., 1999). A more recent survey showed that 22.3% of the dogs were neutered, but did not report males and females separately (Statistics Sweden, 2012). Neuter status could potentially have a confounding effect on the association between sex and SJD/CLD if more females than males were neutered in the study population.

5.2.3 Age, size, and cruciate ligament disease

The median age at the first CLD claim during the study period was 7.1 years, which is comparable to the reported mean and median ages of 4.3 to 8.1 in other studies (O'Neill *et al.*, 2021; Boge *et al.*, 2019; Taylor-Brown *et al.*, 2015; Guthrie *et al.*, 2012; Adams *et al.*, 2011; Harasen, 2008; Necas *et al.*, 2000). An association between breed size and age at diagnosis/euthanasia was observed: most of breeds that were old at diagnosis/euthanasia were small or medium sized, while most that were young at diagnosis/euthanasia were large or giant sized. This correlates well with previous reports, although only a few studies have investigated this association (Duval *et al.*, 1999; Whitehair *et al.*, 1993). For example, in a study of CCLD in dogs under two years of age, all high-risk breeds were large or giant (Duval *et al.*, 1999). In contrast, various small breeds were included in the high-risk group in studies that included dogs of all ages, including Paper II in this thesis (Taylor-Brown *et al.*, 2015; Witsberger *et al.*, 2008; Whitehair *et al.*, 1993). Despite differences in study design and study population, this indicates that small breeds are diagnosed at a higher age than larger breeds. Vasseur *et al.* (1985) examined degenerative changes in the CCLs of different-sized dogs with no signs of SJD and found that the changes appeared at a younger age in dogs weighing over 15 kg than in those weighing less than 15 kg. Future studies should investigate the background of these degenerative changes and why they appear earlier in large sized breeds, as prevention of these changes could result in a dramatically lowered incidence of CCLD.

Figure 14. English bulldog, one of the breeds at high risk of being diagnosed with cruciate ligament disease at a young age. Photo: Julia Gyllenadler

It should be noted that the age at diagnosis in different breeds also is affected by the general health status and longevity of the breed. The English bulldog (Figure 14), which was significantly younger at CLD diagnosis, has a reported median longevity of only 7.2 to 8.4 years (O'Neill *et al.*, 2019b; O'Neill *et al.*, 2013). This contrasts sharply with the border terrier and the West Highland white terrier, both of which were significantly older at CLD diagnosis (Paper II), and have a reported median longevity of 12.7 and 13.4 years, respectively (O'Neill *et al.*, 2019a; O'Neill *et al.*, 2017). Thus, a low age at diagnosis within a breed may be a result of either an early disease debut or a short longevity within the breed (such as in the English bulldog), or both. In other words, some dogs within the breed die/are euthanized due to other conditions before the age when CLD would debut. A general trend of shorter lifespans in larger dogs than in smaller has also been described; increasing body weight is negatively correlated with longevity (O'Neill *et al.*, 2013). Thus, a larger dog may be perceived as older at a younger age than a smaller dog, which may affect the owners' decision about euthanasia.

5.2.4 Concurrent disease

About two thirds of the dogs with veterinary care insurance claims for CLD had prior claims for other diagnoses. Diagnoses within some organ systems were more common in dogs with CLD than in the rest of the dog population. These included the musculoskeletal, dermatologic, gastrointestinal, urogenital, ophthalmic, and hepatic organ systems as well as other, more general, diagnoses affecting the whole body such as fatigue. Some disorders in these organ systems or their associated treatments might predispose dogs to CLD, but the retrospective study design precluded causal inference. It is also possible that some diagnoses shared common risk factors, such as breed or age, with CLD, which could lead to the observed association even if there were none. That many dogs had previous or concurrent comorbidities is important, as these comorbidities might have affected their prognosis for return to adequate function, their recovery after treatment, and the veterinarian or owner's recommendation or decision about treatment. For example, the most common non-orthopaedic disorder was dermatologic disease, which might have increased the risk of SSIs in dogs surgically treated for CLD and concurrently affected by pyoderma.

5.3 Severe postoperative complications

The most common severe postoperative complications were related to surgical implants or SSIs. The overall frequency of severe postoperative complications was 25.1%, but it varied by surgical technique. The frequency of complication after TPLO in our data was higher than that of major complications after TPLO surgery reported in previous studies (31.2% vs. 3.1–27.8%; Hans *et al.*, 2017; Coletti *et al.*, 2014; Garnett & Daye, 2014; Christopher *et al.*, 2013; Fitzpatrick & Solano, 2010). The frequency of severe postoperative complications following TTA was 24.6%, which is in the range of 6.5% to 38.9% previously reported for major complications (Costa *et al.*, 2017; Hans *et al.*, 2017; Christopher *et al.*, 2013; Hirshenson *et al.*, 2012; Wolf *et al.*, 2012; Dymond *et al.*, 2010; Lafaver *et al.*, 2007). The frequency after LFS was 22.0%. However, comparisons could not be made to previous studies of complications after LFS surgery, since these lack classification of complication severity (Gordon-Evans *et al.*, 2013; Nelson *et al.*, 2013; Casale & McCarthy, 2009).

Tibial plateau levelling osteotomy had the highest occurrence of severe postoperative complications, but was associated with a significantly lower hazard of such complications than LFS when the confounding effects of age and body weight were adjusted for in the multivariable Cox proportional hazards model. The median body weight of the dogs treated with TPLO was remarkably higher than that of the dogs treated with LFS and TTA (42.2 kg vs. 11.7 kg and 29.0 kg, respectively). High body weight is a commonly reported risk factor for postoperative complications after surgical treatment of CCL rupture, which correlates well with the results in Paper III (Coletti *et al.*, 2014; Wolf *et al.*, 2012; Steinberg *et al.*, 2011; Taylor *et al.*, 2011; Fitzpatrick & Solano, 2010; Casale & McCarthy, 2009; Tuttle & Manley, 2009). Younger age was also associated with increased hazard of severe postoperative complications. Problems with activity restriction during the postoperative period in young, active dogs and heavy dogs likely contributed to these increased hazards, as did the increased mechanical load on the implants in heavy dogs. This demonstrates that both the surgical technique and the patient's age and body weight should be considered when assessing the risk of severe postoperative complications.

Differences in various classification of complications make in between-studies comparisons of complication occurrence and severity difficult. Classification of complication severity is complex and can be based on several factors. These include the complication's impact on the patient's health, welfare, and recovery; the caregiver's emotional, labour and economic burdens; and the use of antibiotics, since antimicrobial resistance is one of the major threats to public and animal health (Swedish Medical Products Agency, 2016). The definition by Cook *et al.* (2010) used in Paper III has been used in several other studies of complications related to CCLD surgery (Costa *et al.*, 2017; Danielson *et al.*, 2016; Christopher *et al.*, 2013). Various recent studies, however, have used other definitions of major complications, such as (1) those that require surgical intervention, (2) those that result in lameness for more than 12 weeks or lameness of unknown origin, and/or (3) those that involve implant failures or fractures (Peress *et al.*, 2021; Chiu *et al.*, 2019; Coletti *et al.*, 2014; Garnett & Daye, 2014; Wolf *et al.*, 2012; Fitzpatrick & Solano, 2010). The broader definition of severe complications in Paper III may explain its higher finding of complication occurrence that in other studies, although it may represent a truly higher occurrence of severe postoperative complications.

The definition by Cook *et al.* (2010) was modified in Paper III: skin irritations in the area clipped for surgery that were treated with local antibiotics and mild lameness that resolved with analgesic treatment were classified as minor, rather than major, complications. These complications had the characteristics of a minor complication, but included a medical treatment, and thus should have been classified as major according to the definition. This would have biased the results towards a false high rate of severe postoperative complications; however, deviations from the recommended criteria for classification of complications further aggravate comparisons of complications between studies, as the purpose of the criteria is consistent reporting (Cook *et al.*, 2010).

5.4 Euthanasia related to cruciate ligament disease

In total, 8.5% of the dogs with CLD claims and concurrent life insurance had life insurance settlements due to CLD (Paper II). The median time from diagnosis to CLD-related euthanasia was only 7 days, but varied up to 4.25 years. The fact that some dogs had several months or years between diagnosis and euthanasia may indicate that treatment failures occur and result in euthanasia. This is in line with the results from Paper IV, where 18.3% of the dogs were euthanized due to CCLD sometime after treatment initiation. In total, 27.8% of the dogs at the hospitals with CCLD were euthanized due to CCLD at diagnosis or during the follow-up period. Thus, the percentage of dogs euthanized for disease-related causes was much higher at the hospitals (27.8%) than in the insurance database (8.5%). This discrepancy may be explained by several factors. Although most of the dogs euthanized because of CCLD at the University Animal Hospital in Uppsala were assigned the diagnostic code ‘Cruciate ligament rupture’, some were assigned the unspecific code ‘Death/euthanized’ or a code associated with a comorbidity. Thus, the cause-specific mortality rate in the Agria Pet Insurance database is probably slightly underestimated, since some CLD-related deaths were likely reported under other diagnostic codes. It is possible that the cases at the hospitals were more complicated than the general CCLD case, since the hospitals were referral hospitals, and that euthanasia was performed more often in these cases. In addition, the follow-up period in the hospital-based studies was longer, which made it possible to register deaths that occurred after 2016, while the observation period for the insurance-based studies ended in 2016. Finally, the life insurance terminated at eight, ten, or 12 years of age (depending on breed), and thus CLD-related deaths that occurred at a higher age were not registered in the insurance database.

Several large and giant sized breeds, including the dogue de Bordeaux, cane corso, and Newfoundland, had increased risk of CLD-related euthanasia in Paper II. This correlates well with the results of Paper IV, where heavier dogs had increased risk of CCLD-related euthanasia, and it indicates that smaller dogs have better outcomes after CCLD treatment. Conservative treatment was associated with a higher hazard of CCLD-related euthanasia than treatment with osteotomy procedures (Paper IV). This is in line with a previous study that reported better clinical outcomes after TPLO than conservative treatment (Wucherer *et al.*, 2013). However, studies of outcomes after conservative treatment of CCLD in dogs are scarce and more research in this area is warranted.

The decision to euthanize is complex and influenced by many factors. Both Sweden and Norway have animal welfare legislation that is more stringent and has generally higher requirements than in many other European countries (Veissier *et al.*, 2008). Lameness is generally considered a welfare concern in both Sweden and Norway, and it may result in a decision to euthanize in severe cases. This may limit the generalizability of the results regarding disease-related euthanasia to dog populations in other countries.

5.5 Methodological considerations

5.5.1 Insurance data

Although insurance data are valuable for companion animal research, some limitations should be mentioned. Ideally, the information in the database should have been validated against medical records to confirm the assigned diagnoses of the claims. However, this was not possible as the General Data Protection Regulation precluded access to the medical records. Even though the diagnosis of CLD is quite straightforward, there is risk that some cases were reported under less specific diagnostic codes such as ‘Lameness’. In addition, there is a risk that the cost of treatment in some of the conservatively managed dogs was lower than the deductible of the insurance. The same is valid for dogs with low grade PLs associated with mild clinical signs, which may not even have been presented to a veterinarian. Thus, the IR of SJD and CLD may be slightly underestimated, and conservatively treated dogs may be less well represented than surgically treated dogs. This could also affect the distribution of diagnoses and the IR and RR for SJD and CLD within the breeds if some breeds were conservatively treated more often than others (e.g., small dogs with CLD).

The insurance database covered around 38% of the Swedish dog population during the study period. Due to the large number of included dogs, even small differences in RRs can be statistically significant. Therefore, it is important to consider the magnitude of the differences when the RRs are interpreted. The width of the confidence intervals can be used to assess the precision of the estimates.

Insured dogs had higher odds of CCLD, PL, and OA than uninsured dogs in study populations in England and UK, which may be a result of limited funds in owners of uninsured dogs (Anderson *et al.*, 2018; O'Neill *et al.*, 2016; Taylor-Brown *et al.*, 2015). It is not known whether the same is true in Sweden, but in contrast to many countries around 90% of the Swedish dog population is insured (Agria Pet Insurance, 2017). Therefore, the study population in Papers I and II is probably representative for the general Swedish dog population. In contrast to the high insurance coverage in Sweden, only around 1% to 2% of dogs and cats in the US are insured, and around 50% in the UK (Mills, 2019; Jenks, 2017). The results in Papers I and II are probably generalizable to insured dogs in countries with lower insurance coverage than Sweden, but their generalizability to uninsured dogs might be limited, given the higher odds of disease reported in insured versus uninsured dogs in previous studies (Anderson *et al.*, 2018; O'Neill *et al.*, 2016; Taylor-Brown *et al.*, 2015).

5.5.2 Medical records

The dogs were not randomly assigned to undergo a specific treatment as the studies were retrospective. Although factors that could have affected the treatment outcome such as body weight, age, and concurrent diseases were included in the statistical analyses, other factors such as the owners' economy and the preferences of the examining veterinarians probably influenced the treatment decisions and possibly also the outcomes. In addition, the information in the medical records varied, which precluded detailed description of the implant-related complications. Some complications might also have been missed due to recall bias during the telephone interviews with the dog owners. No clinical assessment of treatment outcomes was performed, which is acknowledged as a limitation. However, a clinical follow-up might have biased the results towards a more favourable outcome if the dogs that were euthanized due to CCLD were excluded from the assessment.

The total effect of the treatment on the hazard of severe postoperative complications and survival was estimated. Thus, the effects of intervening variables such as postoperative antibiotics and physiotherapy were integrated into the total effect of the treatment and not evaluated separately. To assess the effect of postoperative antibiotic administration, a study with a prospective, standardized, and randomized design would be necessary.

Evidence in the literature for the effect of the surgeon's level of experience on postoperative complications is in conflict; some studies found higher rates of both general complications and SSIs after surgeries performed by less experienced surgeons (Lopez *et al.*, 2018; Christopher *et al.*, 2013), while others found no such association (Gordon-Evans *et al.*, 2013; Casale & McCarthy, 2009; Pacchiana *et al.*, 2003). The experience level of the surgeons had no significant impact on the hazard of severe postoperative complications (Paper III). It is possible that categorizing the surgeons as board-certified, resident, and experienced was inappropriate and that misclassification bias was introduced since the experience level in each category might have varied both in total and for the different surgical techniques. However, any introduced misclassification bias was likely nondifferential.

Body weight was identified as an important risk factor for both severe postoperative complications and CCLD-related euthanasia. It is important to consider that the effect of each treatment is valid only in the body weight range of the dogs that received the treatment, and cannot be extrapolated to dogs of other weight classes. For example, only medium to giant sized dogs were treated with TPLO, and thus the outcome of TPLO for small dogs is unknown.

Longer duration of anaesthesia or surgery has been associated with increased risk of SSI in some studies (Yap *et al.*, 2015; Eugster *et al.*, 2004;

Brown *et al.*, 1997), but not in others (Valkki *et al.*, 2020; Aiken *et al.*, 2015). The durations of anaesthesia and surgery were not consistently registered in the medical records at the two university hospitals during the study period and could therefore not be included in the analysis in Paper III, which is acknowledged as a limitation. The median duration of the anaesthesia for the TPLO procedures, however, was longer than reported in other publications (Clark *et al.*, 2020; Hagen *et al.*, 2020; Coletti *et al.*, 2014; Fitzpatrick & Solano, 2010). This could be due to different routines for postoperative radiographs, which were generally taken and assessed by a radiologist during the same anaesthetic event, resulting in a longer duration of anaesthesia.

Treatment of concurrent meniscal injury in dogs with CCLD has been extensively evaluated in the literature. Some authors describe evaluating and treating concurrent meniscal injury in dogs with CCLD as imperative for achieving optimal recovery and function (Franklin *et al.*, 2018), while others question the need for routine meniscal examination in all dogs surgically treated for CCLD (Jandi & Schulman, 2007). Meniscal injuries at the two hospitals were treated at the discretion of the responsible surgeon, and the level of information in the medical records precluded detailed descriptions of meniscal injury treatments. However, meniscal release was not performed at the hospitals during the study period. Arthrotomy or arthroscopy was performed during all TPLO procedures and most LFS procedures, but only in around 55% of TTA procedures; evaluation of concurrent meniscal injury was not, therefore, performed to the same extent for all surgical techniques. At Hospital 1, where the TTAs were performed, arthrotomy/arthroscopy was performed if meniscal injury was suspected based on the clinical examination findings. There is a risk that undiagnosed meniscal injuries affected the results of the studies, i.e., that some of the dogs euthanized due to persistent lameness had undiagnosed meniscal injuries. According to a review by McCready and Ness (2016b), there are no high-quality studies that report a direct, causal relationship between meniscal injury and stifle morbidity in clinical cases. Thus, more studies are warranted.

6. Conclusions

- Cruciate ligament disease and PL were the most common SJDs, followed by unspecific diagnoses such as pain from the stifle joint.
- There was a clear distinction between the breeds that contributed the highest number of SJD cases and the breeds that were at high risk of SJD.
- The majority of the breeds with increased risk of CLD were large or giant sized, although breeds of all sizes were affected. Eight of the ten breeds at highest risk of CLD were molosser types. All breeds with increased risk of euthanasia due to CLD were large or giant.
- Age at diagnosis/euthanasia and size of the breed were associated; the majority of the breeds diagnosed and euthanized at a young age were large or giant, while the majority of the breeds diagnosed and euthanized at an older age were small.
- Dogs treated with TPLO had a lower hazard of severe postoperative complications than dogs treated with LFS. Young age and high body weight were also associated with higher hazard of severe postoperative complications.
- Dogs treated with osteotomy procedures had a lower hazard of CCLD-related euthanasia than conservatively treated dogs. Concurrent orthopaedic comorbidities and increasing age and body weight also increased the hazard of CCLD-related euthanasia.

7. Future perspectives

The results of the included studies raise new questions to be answered in future research.

Why are dogs of the molosser type at high risk of CLD? Is it possible to identify dogs at high risk of CLD and exclude these from breeding programmes?

Eight of the ten breeds with the highest risk of CLD were molosser types, which strongly indicates a genetic component to the aetiopathogenesis of the disease. Studies on the genetic background of CCLD have been performed in various breeds including the Newfoundland, a molosser type (Wilke *et al.*, 2009). Evaluating the genetic background of CCLD allows for the development of statistical models for predicting dogs at high risk of CCLD that can be excluded from breeding programmes. Some work on predictive genetic modelling for CCLD has already been done with promising results, for example, in the Labrador retriever, but more research is warranted (Baker *et al.*, 2020).

Why do large breed dogs develop CLD at a younger age than small breeds?

An association between breed size and age at CLD diagnosis was identified; breeds diagnosed at a young age were generally large or giant, while breeds diagnosed at older ages were small. This is likely a result of an earlier onset of the degenerative process in the stifle joints of these large breeds. An important step in the process of preventing CLD would be to identify why the degenerative process starts at such a young age in these large breeds.

What is the clinical outcome after conservative treatment of CCLD?

Dogs that were conservatively treated for CCLD had a higher risk of CCLD-related euthanasia (Paper IV). However, the results did not include an evaluation of the clinical outcome. Conservative treatment is still widely used in small dogs (≤10–15 kg), but there is limited information about the treatment result. Further studies of the clinical outcomes of conservative treatment for CCLD, especially in small dogs, are warranted.

Can data from medical records and insurance data be combined?

Medical records and insurance databases are both valuable resources for epidemiologic research, but both have limitations related to data collection and registration (described in the Introduction). Detailed data on disease characteristics, treatments, and outcomes from medical records in combination with population-based data from the insurance database would be ideal for evaluating both disease occurrence at the population level and details related to treatments and outcomes. It would also enable continuous validation of the insurance data against data in the medical records. Such data from several countries could further be combined, although differences in the insurance coverage of different dog population need to be taken into consideration.

Can regenerative methods be used for CCLD treatment?

Regenerative medicine is an emerging field that includes cell therapy and aims to restore normal function. For CCLD in particular, regenerative medicine involves methods for cruciate ligament repair and for slowing the progression of OA in the affected joint (Perrone *et al.*, 2018). These methods differ from currently available treatment methods, which aim to stabilize the stifle without replacing or enhancing the healing of the ligament (Perrone *et al.*, 2018). The regenerative treatment methods are still under evaluation and not yet in use for CCLD treatment in dogs, but they may be an important part of CCLD treatment in the future, alone or in combination with other therapies (Perrone *et al.*, 2018).

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Popular science summary

The knee joint is an important part of a dog's locomotor system. The joint can suffer from many different diseases, and cruciate ligament disease is often reported as the most common. The cranial cruciate ligament is important for the stability of the joint, and rupture of the ligament results in joint instability. The treatment usually involves a complicated and costly surgical procedure, but the disease can also be treated conservatively, i.e., with physiotherapy, analgesia, rest, and weight loss if indicated. Although the treatments are often described as successful, it is not uncommon for dogs to have chronic pain and lameness. It is unknown how often the disease results in euthanasia and which factors affect dogs' survival after the diagnosis of cruciate ligament disease. The aim of this thesis was to investigate the epidemiology of knee joint disease, with a special focus on cruciate ligament disease, and to evaluate treatment outcomes in dogs with cruciate ligament disease.

Data from Agria Pet Insurance was used to evaluate the epidemiology of knee joint disease and cruciate ligament disease. Cruciate ligament disease and patellar luxation were the most common knee joint diagnoses among the approximately 600,000 dogs included in the insurance database. Female dogs had a higher risk of both knee joint disease in general and of cruciate ligament disease. Cruciate ligament disease affected breeds of all sizes, but mostly large sized breeds, while patellar luxation mainly affected smaller breeds. The American bulldog, boerboel, Presa Canario, dogue de Bordeaux, and English bulldog had the highest risks of both knee joint disease in general and cruciate ligament disease. The cruciate ligament disease was usually diagnosed around the age of seven years. An association between age at diagnosis and breed size was seen; dogs diagnosed early in life were usually large, while dogs diagnosed later were small. Several breeds, including dogue de Bordeaux, cane corso, Newfoundland, Rottweiler, and boxer had a higher risk of euthanasia due to cruciate ligament disease.

The assessment of the treatment outcome included evaluating severe postoperative complications and survival in dogs diagnosed with cruciate ligament disease at two university animal hospitals in 2011–2016. The medical records of dogs with cruciate ligament disease were reviewed and information on their history, breed, age at diagnosis, sex, treatment, complications, and survival was recorded. The database included 436 dogs with 501 affected knee joints, since some dogs were affected on both hind legs. The dogs were treated either with surgery, including several different techniques, or conservatively. In total, 25.1% of the dogs suffered from severe postoperative complications, most often within a month after the surgery. The most common types of severe postoperative complications were related to the surgical implants or wound infections. Joints treated with TPLO had significantly lower risk of severe postoperative complications than those treated with LFS. In addition, the risk was lower for older dogs than younger, and it increased with increasing body weight. This may be due to the higher mechanical load on the knee joints in heavy dogs and problems with restricted activity after the surgery in young and active dogs.

Of the dogs included in the survival study, 61 (18.3%) were euthanized due to CLD. Some dogs had other concurrent diagnoses that contributed to the decision to euthanize. The most common reasons for cruciate ligament-related euthanasia were persistent lameness and CLD on the other hindlimb. Dogs treated with osteotomy procedures had a significantly lower risk of CLD-related euthanasia than conservatively treated dogs. In addition, the risk of CLD-related euthanasia increased with increasing age and body weight, and it was higher for dogs with other concurrent orthopaedic diseases.

Information about breeds at increased risk of disease and the advantages and disadvantages of different treatment options is important for veterinarians in their daily work, but also for pet owners who are faced with choosing a treatment for a dog with CLD.

Populärvetenskaplig sammanfattning

Knäleden är en viktig del av hundens rörelseapparat. Leden kan drabbas av många olika sjukdomar, där korsbandsskada ofta rapporteras vara den vanligast förekommande sjukdomen. Korsbanden bidrar till ledens stabilitet och korsbandsruptur leder till att leden blir instabil. Behandlingen involverar i regel ett komplicerat och kostsamt kirurgiskt ingrepp, men sjukdomen kan även behandlas konservativt d.v.s. med sjukgymnastik, smärtlindring, vila och vid behov även viktnedgång. Även om behandlingsresultatet ofta beskrivs som lyckat så är det inte ovanligt att de drabbade hundarna får problem med kronisk smärta och hälta. Det är okänt hur vanligt det är att sjukdomen resulterar i avlivning och vad som påverkar överlevnaden efter en korsbandsskadediagnos. Målet med avhandlingen var att undersöka knäledssjukdomarnas epidemiologi, med särskilt fokus på korsbandsskada och att utvärdera behandlingsresultatet hos hundar med korsbandsskada.

Data från Agria Djurförsäkring användes för att utvärdera knäledssjukdomarnas och korsbandsskadornas epidemiologi. Korsbandsskada och patellaluxation var de vanligaste knäledsdiagnoserna bland de cirka 600,000 hundar som var försäkrade hos Agria Djurförsäkring under studieperioden. Tikar hade högre risk för både knäledssjukdom generellt och korsbandsskada. Korsbandsskada drabbade raser av alla storlekar, även om stora raser var överrepresenterade, medan patellaluxation främst drabbade raser av mindre storlek. De raser som hade högst risk för att drabbas av både knäledssjukdom generellt och korsbandsskada var amerikansk bulldogg, boerboel, dogo canario, dogue de bordeaux och engelsk bulldogg. Korsbandsskadan diagnosticerades i regel runt sju års ålder. Ett samband mellan ålder vid diagnos och rasstorlek påvisades; hundarna som diagnosticerades tidigt i livet var i regel av stora raser, medan hundarna som diagnosticerades senare i livet var av mindre raser. Ett flertal raser, bland annat dogue de bordeaux, cane corso, newfoundland, rottweiler och boxer hade ökad risk för att avlivas på grund av korsbandsskada.

Behandlingsresultatet analyserades genom att utvärdera allvarliga postoperativa komplikationer och överlevnad hos hundar med korsbandsskada diagnosticerade vid två universitetsdjursjukhus 2011-2016. Hundarnas journaler granskades och information om historik, ras, kön, ålder vid diagnos, behandling, komplikationer och livslängd registrerades. Databasen inkluderade 436 hundar med 501 drabbade knäleder. Hundarna hade behandlats antingen med operation, där flera olika ingrepp förekom, eller konservativt. Totalt drabbades 25,1% av hundarna av allvarliga postoperativa komplikationer och majoriteten av komplikationerna uppkom inom en månad efter ingreppet. De vanligaste typerna av allvarliga komplikationer var relaterade till de kirurgiska implantaten och sårinfektioner. Knäleder behandlade med tekniken tibial plateau levelling osteotomy hade lägre risk att drabbas av allvarliga postoperativa komplikationer jämfört med knäleder behandlade med lateral fabellotibial sutur. Det visade sig även att risken var lägre för äldre hundar jämfört med yngre och att risken ökade med ökande kroppsvikt. Det kan bero på att belastningen på leden ökar hos tunga hundar och att det är svårare att hålla en ung, livlig hund i stillhet efter ingreppet.

Av de hundar som ingick i överlevnadsstudien avlivades 61 (18,3%) på grund av sin korsbandsskada. Vissa hundar hade andra samtidigt förekommande diagnoser som bidrog till beslutet om avlivning. De vanligaste orsakerna till korsbandsrelaterad avlivning var kvarstående hälta och korsbandsskada på andra benet. Risken för avlivning var högre för de hundar som behandlats konservativt jämfört med hundar som behandlats med osteotomiingrepp och ökade med stigande ålder och ökande vikt. Dessutom var risken för avlivning högre för hundar som hade andra samtidigt förekommande ortopediska sjukdomar.

Information om vilka raser som har högre eller lägre risk för sjukdom och fördelar och nackdelar med olika behandlingsalternativ är viktig kunskap för veterinärer i deras dagliga arbete, men även för djurägare som står inför val av behandling för en hund med korsbandsskada.

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Vet Record

ORIGINAL RESEARCH

The epidemiology of stifle joint disease in an insured Swedish dog population

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Abstract

Background: Stifle joint diseases (SJD) are common in dogs and include a variety of diagnoses. The objective of the study was to provide an overview of the epidemiology of SJD in insured dogs.

Methods: An historical single cohort study of dogs insured in Agria Pet Insurance (2011–2016) in Sweden was performed. Incidence and relative risk (RR) of SJD was calculated for the whole dog population and for subgroups divided by breed, breed group and sex.

Results: The study population included almost 600,000 insured dogs (>1.7 million dog-years). Ninety-three different stifle joint diagnoses were reported in 9624 dogs, and the most common were cruciate ligament rupture and patellar luxation. The incidence of SJD was 55.4 cases per 10,000 dog-years at risk. Bulldog and boerboel had the highest RR of SJD. The breeds that accounted for the highest proportion of all SJD claimed dogs were mixed breed and Labrador retriever. Female dogs had a slightly increased RR compared with male dogs (RR 1.06, $p = 0.006$). The incidence increased yearly during the observation period.

Conclusion: The study demonstrates breed-specific differences in incidence of SJD in dogs, which may be of importance for breeders, dog owners and veterinarians.

INTRODUCTION

Stifle joint diseases (SJD) include a variety of diagnoses such as cranial cruciate ligament disease (CCLD), patellar luxation (PL), osteochondrosis (OC) and osteoarthritis (OA), which are among the most common musculoskeletal disorders in dogs.[1] Most of these disorders are painful, have their onset in young or middle-aged dogs and often become chronic, potentially affecting a considerable percentage of the lifespan in affected individuals.[2–9] Available treatment options include advanced surgical procedures, which can be costly for the animal owner. For example, it was estimated that the annual cost for treatment of CCLD in dogs in the US during 2003 was 1.32 billion dollars.[10]

Risk factors for development of SJD as a composite diagnosis has not been previously evaluated at a population level, but risk factors for CCLD and PL have been explored in previous studies. Cranial cruciate ligament disease generally affects middle-aged to older dogs, and predisposed breeds include Newfoundland, Labrador retriever and Rottweiler.[3,11,12] Patellar luxation generally affects young dogs and small breeds such as Chihuahua, miniature pinscher, Pomeranian and Yorkshire terrier.[4,13]

Measures of SJD burden such as prevalence and incidence are necessary for assessing the importance of these disorders at a population level. The data used for such calculations need to include sufficient information about both the disease cases and the general population.[14] Insurance data are excellent for monitoring disease occurrence, when databases are large enough to enable studies with high statistical power.[14] In Sweden, it was estimated that 77% of the dog population had veterinary care insurance during 2012, and during 2016 approximately 38% of the dog population was insured in Agria Pet Insurance ([15], P. Olsson, personal communication). The insurance database has been used in many epidemiological studies on conditions such as intervertebral disk degeneration, atopic dermatitis, dystocia and adrenocortical insufficiency.[16–19] A validation of Agria Pet Insurance database against practice records performed previously showed excellent agreement for sex, breed and for 85% of diagnoses, and fair agreement for birth date with a tendency of better agreement for clinics with computerized medical records.[20] The agreement is likely better today since computerized medical records are used to a higher extent, and more recent studies reported excellent and acceptable agreement for epilepsy and atopic dermatitis diagnoses.[21,22]

Most of the previous studies evaluating the epidemiology of SJD in dogs are based on data from veterinary teaching hospitals and primary-care veterinary practices.[1,3,4,11,13,23,24] However, most of these estimates reflect only proportions of clinic patients, which may not reflect actual rates and may not be generalizable to the wider dog population. The reported prevalence for SJD varies; for CCLD between 0.56 and 2.55%[3,11,23,24] and for osteochondrosis between 0.02 and 0.06 %.[1,13] The prevalence for PL has been estimated from 1.3 % up to 12–23.6% in certain breeds, based on data from primary-care veterinary practices and PL screening programs.[4,25–27] The variation in estimates for each condition may be a result of methods of calculation and diverse study populations, ranging from dogs included in screening programs to dogs attending primary-care veterinary clinics and referral Veterinary Teaching Hospitals.

The objective of the current study was to provide population-based estimates of incidence and relative risk (RR) for all included dogs and in subgroups by breed and sex, by conducting an exploratory cohort study using data from Agria Pet Insurance in Sweden (Agria Djurförsäkring, Stockholm, Sweden). Further aims were to present proportional distribution of the different stifle joint diagnoses within the breeds most commonly presenting with SJD and to calculate the yearly incidence of SJD.

MATERIALS AND METHODS

Data

An historical, exploratory single cohort study of dogs with veterinary care insurance in Agria Pet Insurance in Sweden between 1 January, 2011 and 31 December, 2016 was performed. The data included variables on sex, breed, birth year, date when the dog entered or left the insurance program, age at start of the observation period or at insurance enrollment, diagnostic codes for veterinary care claims (if any) and date when the claim was registered in the database. The dogs could be enrolled in veterinary care insurance at any age. Dogs were classified as either female or male; information about neuter status was not available. The breed and breed group variables were based on the classifications by the Federation Cynologique Internationale (FCI) and the Swedish Kennel Club (SKC). Non-purebred dogs were classified as mixed breeds and put into a separate breed group (breed group 11). Seven breeds were non-approved by both the FCI and the SKC and allocated to the following breed groups: Old English bulldog, American bulldog and boerboel to breed group 2, pitbull terrier to breed group 3, Alaskan husky and hedehund to breed group 5 and griffon à poil laineux/boulet to breed group 7. All available breeds were included in the analysis.

Diagnostic codes were assigned by the attending veterinarians based on the hierarchical diagnostic registry developed by the Swedish Association of Veterinary Clinics and Hospitals and used by veterinarians in Sweden since January 1995.[28] For some diagnoses, the insurance company applied additional conditions before a claim was registered, for example continuous insurance since before the age of 4 months (PL, OC and degenerative joint diseases). Claims for degenerative joint diseases could be registered in dogs enrolled at a higher age, but only following a waiting period of 12 months after enrollment. The claims were registered when the total cost of the veterinary appointment(s) during a 125-day period exceeded the deductible of the insurance. The deductible and the maximum annual reimbursement were chosen by the owner upon enrollment in the insurance program. Claims for diseases that were present before insurance enrollment were excluded by the company. The date of and age at diagnosis were based on the claim date. If an owner simultaneously submitted several receipts from different veterinary appointments, the appointments were usually coded in separate claims but for the same date, with one or two diagnosis per appointment. Dogs were excluded when information about birth year, breed, sex, age or date of enrollment was missing or uncertain.

Analysis

Data analysis was performed in RStudio version 1.2.1335.[29] Summary statistics for continuous variables are presented as median (range) and categorical as percentage. Two-sided one sample z test of proportions was used to compare the proportions of female and male dogs. Dog-years at risk (DYAR) were calculated from the start of the insurance policy (if insured at/after 1 January, 2011) or start of observation period (if insured before 1 January, 2011) to the date of the first stifle joint claim during the observation period in dogs with stifle joint claims or end of insurance/the end of observation period (31 December 2016 or withdrawal from insurance) in dogs without stifle joint claims.

The first SJD claim during the study period for each affected dog was registered for calculation of incidence. There was no information about claims before the start of the observation period for dogs insured before 1 January, 2011. Incidence during the observation period is expressed as the number of dogs with SJD per 10,000 DYAR. Relative risk was calculated by dividing the incidence for the subgroup of interest (e.g. breed or breed group) by the incidence of the rest of the population (with the subgroup of interest excluded). Confidence intervals (CI) were based

TABLE 1 Incidence and relative risk of stifle joint diseases (SJD) for the 15 breeds accounting for the highest proportion of the 9624 dogs with stifle joint claims, among dogs insured in Agria Pet Insurance during 2011–2016

	Breed	Incidence per 10,000 DYAR (CI)	Relative risk[a] (CI)	% of SJD claimed dogs
1	Boxer	195 (166–227)	3.56 (3.04–4.15)	1.72
2	Staffordshire bull terrier	167 (145–192)	3.06 (2.64–3.52)	2.04
3	Bichon frise	167 (143–192)	3.04 (2.61–3.52)	1.90
4	Yorkshire terrier	163 (142–187)	2.99 (2.59–3.42)	2.19
5	Rottweiler	162 (145–180)	2.98 (2.66–3.33)	3.40
6	Cairn terrier	160 (137–186)	2.93 (2.50–3.41)	1.75
7	French bulldog	130 (113–150)	2.38 (2.05–2.74)	2.04
8	Bichon Havanais	106 (89.9–123)	1.92 (1.63–2.25)	1.66
9	Chihuahua	93.8 (84.5–104)	1.72 (1.55–1.91)	3.84
10	Poodle miniature & toy	82.0 (70.5–94.9)	1.49 (1.28–1.73)	1.88
11	Labrador retriever	57.0 (51.7–62.7)	1.03 (0.93–1.14)	4.40
12	Jack Russell terrier	56.0 (49.1–63.6)	1.01 (0.89–1.15)	2.47
13	German shepherd dog	53.7 (48.1–59.8)	0.97 (0.87–1.08)	3.46
14	Mixed breed	50.7 (48.6–53.0)	0.89 (0.85–0.94)	21.4
15	Golden retriever	50.1 (44.6–56.1)	0.90 (0.80–1.01)	3.14

[a]Relative to the rest of the population (with the breed excluded).
Abbreviations: CI, 95 % confidence interval; DYAR, dog-years at risk.

on the Poisson distribution and calculated with the R-package 'exactci' (version 1.3-3).[30] The diagnostic codes were classified into 14 categories (Table S1). Bar plots of the distribution of diagnoses within breeds were generated with the R-package 'ggplot2' (version 3.2.1).[31] Every dog was included only once in each diagnostic category. Bonferroni correction for multiple comparisons was used to adjust the significance level for calculation of RRs for breeds and breed groups and was based on the number of breeds (n = 339) or breed groups (n = 11) included in the comparison. *p*-values < 0.05, after corrections, were considered significant. Breed risks were described using forest plots from the R-package 'forestplot' (version 1.9).[32] Breeds with RR around 1 (range 0.85–1.15, $p > 0.05$ and with a narrow CI ±0.15) were identified, in order to find breeds without either increased or decreased risk of SJD. Yearly incidence was calculated by dividing the number of claimed dogs with the sum of DYAR each year during the observation period.

RESULTS

The study population included almost 600,000 insured dogs. Approximately 700 dogs were eliminated according to the exclusion criteria. During the observation period (2011–2016), the total duration of coverage for all dogs was more than 1.75 million dog-years, and the median duration of the insurance per dog was 2.68 years. There were significantly more males (50.9 %) than females (49.1 %, $p < 0.001$), although the magnitude of the difference was small. The median age at enrollment in veterinary care insurance during the observation period was 15.7 weeks (range 3.4 weeks–17.5 years). However, some dogs were enrolled in insurance before 1 January, 2011, so the overall median age at start of observation was 2.4 years (3.4 weeks-21 years).

In total, 9624 dogs had 22,647 veterinary care claims for SJD. The median age at first stifle joint diagnosis was 5.6 years (7.1 weeks–16.2 years), and the median number of stifle joint claims per SJD-claimed dogs was two (1-32) There are 222 stifle joint diagnoses in the diagnostic registry of which 93 were represented in the database and classified into 14 categories (Table S1). The number of non-reimbursed claims was unknown. The overall incidence of SJD was 55.4 (95 % CI, 54.3–56.5) cases per 10,000 DYAR. Of all dogs with one or more stifle joint claims, 43.5 % had a claim for cruciate ligament rupture, 29.8 % for PL, 21.2 % for pain or unspecific signs from the stifle, 11.6 % for degenerative changes and 6.8 % for arthritis. Each of the following diagnostic categories separately occurred in less than 5% of all dogs with stifle joint claims: traumatic injuries, meniscal injuries, OC, fracture, pain or unspecific signs (patella/fabella), tumour, other malformations and growth disorders, immune-mediated and inflammation (patella/fabella). Of the PLs, 88.7 % were medial, 8.2 % were lateral and 3.1 % were unspecified.

Of the 339 breeds in the database, 230 had at least one dog with a stifle joint claim. The breeds accounting for the highest proportion of all dogs with stifle joint claims were the mixed breed, Labrador retriever, Chihuahua, German shepherd dog and Rottweiler (Table 1).

For distribution of dogs within the diagnostic categories for the twelve breeds accounting for the highest proportion of all SJD claimed dogs, see Figure 1.

There were 25 breeds with an RR significantly above 1 and 24 breeds with a RR significantly below 1 (Figure 2). Four breeds, German shepherd dog, Jack Russell terrier, golden retriever and Labrador retriever

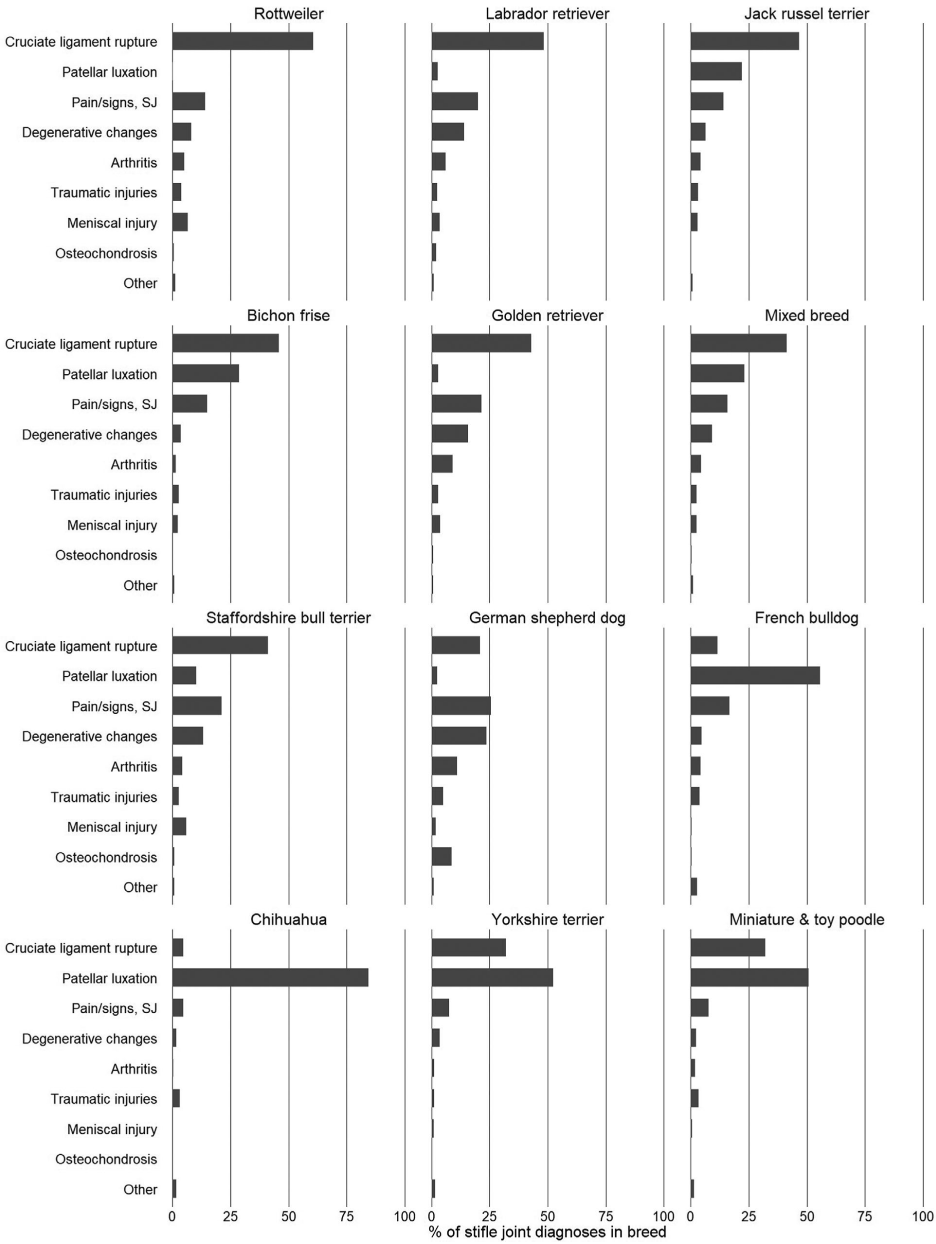

FIGURE 1 The distribution of dogs within the diagnostic categories, for the breeds accounting for the highest proportion of all stifle joint disease claimed dogs. One dog could be included in several diagnostic categories, but only once in each category. Pain/signs, SJ = pain or unspecific signs from the stifle joint

had RRs that were not different from 1 according to the definition in the current study (RR between 0.85–1.15, $p > 0.05$ and a CI ±0.15).

All breed groups had RR significantly different from 1, that is deviated significantly from the average of the rest of the population. Three breed groups had RR over 1; breed group 2, 3 and 9, while the other breed groups had RR below 1 (Figure 3).

Of the dogs with SJD, 50.4% were females, and 49.6% were males, and females were at a slightly higher risk of SJD compared with males (RR 1.06, 95% CI, 1.02–1.10, $p = 0.006$).

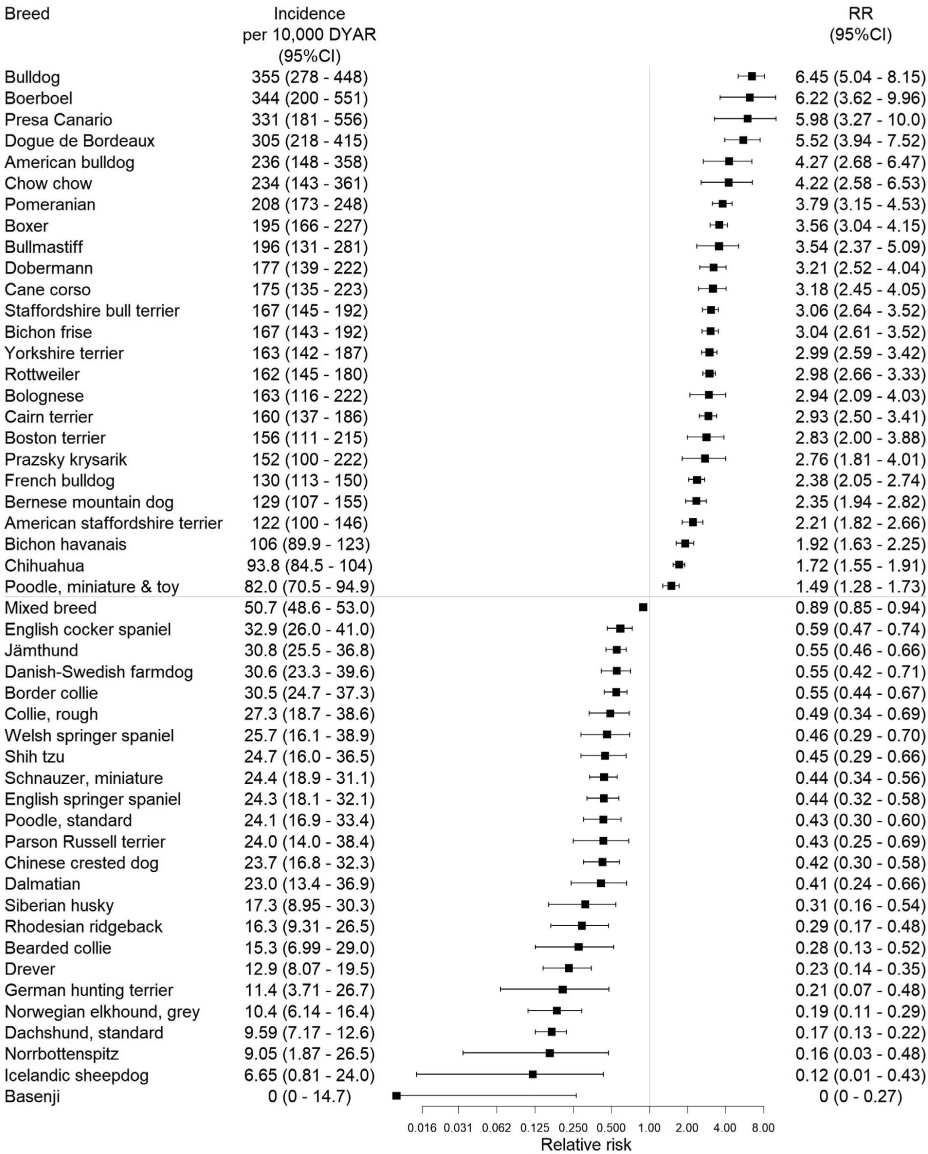

FIGURE 2 The breeds with highest and lowest relative risk (RR) of stifle joint disease (relative to the rest of the population with the breed excluded) in a cohort of dogs insured in Agria Pet Insurance in Sweden during 2011–2016. All RRs were significantly different from 1, after Bonferroni correction. Four breeds, German shepherd dog, Jack Russel terrier, golden retriever and Labrador retriever had RRs that were not different from 1 according to the definition in the current study (RR between 0.85–1.15, $P > 0.05$ and a CI $\pm$ 0.15) and are therefore not included in the figure. A fudge factor of 0.01 was added to the RR of basenji in order to present the RR on the log-scaled x axis. Note that RR = 0.5 means two times decreased risk, RR 0.125 means eight times decreased risk etc.
Abbreviations: CI, confidence interval; DYAR, dog-years at risk.

The yearly incidence of SJD almost doubled from 2011 to 2016 (Table 2). Based on the CI, there was a yearly significant increase in incidence during 2011–2013. Although there was a trend to increased incidence in subsequent years, there was no significant increase from 2014 to 2016.

DISCUSSION

This is the first study to report an epidemiological summary of SJD in insured dogs. The study highlights the importance of reporting not only disease frequencies but epidemiological measurements such

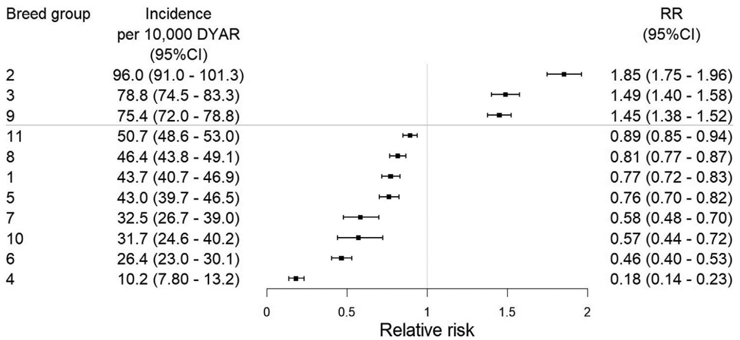

FIGURE 3 Incidence of stifle joint disease by breed group in a cohort of dogs insured in Agria Pet Insurance in Sweden during 2011–2016. All *p*-values for the relative risks (RRs) were significantly different from 1, after Bonferroni correction. The breed groups are: 1. Sheepdogs and cattledogs (except Swiss cattledogs), 2. Pinscher and schnauzer, molossoid and Swiss mountain and cattledogs, 3. Terriers, 4. Dachshunds, 5. Spitz and primitive types, 6. Scent hounds and related breeds, 7. Pointing dogs, 8. Retrievers, flushing dogs, water dogs, 9. Companion and toy dogs, 10. Sighthounds, 11. Mixed breeds. Note that RR = 0.5 means two times decreased risk, RR 0.125 means eight times decreased risk etc. Abbreviations: CI, confidence interval; DYAR, dog-years at risk.

TABLE 2 Incidence of stifle joint disease per 10,000 dog-years at risk (DYAR) in dogs insured in Agria Pet Insurance, the number of claimed dogs, total DYAR and median age in the population each year during the study period (2011-2016)

Year	Incidence (95% CI)	Claimed dogs	DYAR	Median age in population
2011	40.0 (37.7–42.4)	1143	285,500	4.71
2012	52.0 (49.4–54.7)	1513	291,084	4.89
2013	68.6 (65.7–71.6)	2047	298,382	5.08
2014	74.0 (71.0–77.2)	2196	296,570	5.29
2015	77.9 (74.8–81.2)	2278	292,263	5.52
2016	80.4 (77.2–83.8)	2304	286,415	5.68

Abbreviation: CI, confidence interval. Median age in years at 1 January.

as RRs, since there was a clear distinction between the breeds with highest RR of SJD and those that contributed with highest proportion of all dogs with claims for SJD. Common breeds with low or medium risk (e.g., Labrador retrievers and mixed breed dogs in the present study) may present more often to veterinarians due to SJD as a result of the high number of individuals in the population, and thus falsely be interpreted as predisposed to SJD. Of the top five breeds with highest proportion of all dogs with SJD claims, the Rottweiler and Chihuahua also had a significantly increased RR of SJD. In contrast, an uncommon breed with a high risk of disease may have a minor impact on the total veterinary care load. Only 1.7% of all dogs with claims for SJD were of the top five breeds with highest RR (bulldog, boerboel, Presa Canario, Dogue de Bordeaux and American bulldog). Identification of breeds at high risk may be very important for breeders, dog owners and Kennel clubs, as it may support further investigation into other risk factors or breed-specific predispositions and highlight the importance of careful selection for animals for breeding to avoid aggravation of the situation. The discrepancy of the 'top five' lists when assessing incidence, risk or proportion of cases when identifying breeds at risk of disease, stresses the importance of having population-level data as in this insurance material. Misconceptions may arise when studies include only clinic data that do not have an identifiable population-at-risk.

Cruciate ligament rupture was among the top three diagnostic categories in all 12 breeds accounting for the highest proportion of dogs with SJD claims, and the condition affected dogs of all sizes. Patellar luxation on the other hand was among the top two diagnoses for all small breeds among these 12 breeds (Yorkshire terrier, bichon frise, miniature and toy poodles, Jack Russel terrier and Chihuahua), but not even on the top five list for the large breed dogs. This most likely reflects true difference in breed-specific disease patterns; although there may be potential bias from veterinarians' tendency to use a certain diagnostic code based on their understanding of breed predilection.

In addition to cruciate ligament rupture, the top three diagnostic categories in the large breeds included pain or unspecific signs from the stifle joint and degenerative changes. The underlying condition in dogs with claims for pain or unspecific signs from the stifle joint could be an acute, mild injury resolving before a diagnosis is established. However, it is also possible that the clinical signs of these dogs were associated with a specific diagnosis that could not be detected since further diagnostics were not performed, or that the dog received a more specific diagnosis later on. For example, the cranial drawer test that is used to diagnose CCLD can be negative even though the ligament is ruptured, and stifle joint instability is best diagnosed during general anaesthesia.[33,34] Some of the conditions, for example OC and OA, require radiography and/or arthroscopy for diagnosis. This may be declined by the owner, for reasons such as financial constraints, or due to concurrent disease precluding anaesthesia. Cranial cruciate ligament disease is a complex condition described as an 'organ failure' of the stifle joint resulting in lameness, pain and dysfunction, and OA is usually present in stifle joints with CCLD.[35–38] Thus, it is likely that many dogs with claims for cruciate ligament rupture, degenerative changes and pain or unspecific signs from the stifle joint had the same underlying condition: an 'organ failure' of the stifle joint with unconfirmed cause. The fact that diagnoses involving pain and unspecific signs from the stifle joint were so common illustrates the importance of including all diagnoses in the current study, since dogs with such claims also contribute valuable information about the incidence of SJD in dogs.

Patellar luxation was the most common diagnosis in the Chihuahua, Yorkshire terrier, miniature and toy poodle and French bulldog, and the second most common diagnosis after cruciate ligament rupture in the bichon frise and Jack Russell terrier. This is in line with a previous study suggesting that PL is associated with small body size and particularly small leg size.[39] In addition, all of these breeds are reported to be at increased risk of medial PL (MPL).[4,13,40] The fact that cruciate ligament rupture was among the top three diagnoses in all of these breeds could partly be due to the anatomical deviations associated with MPL, such as excessive internal rotation of tibia, which are suggested to increase the risk of CCLD.[36] In one study 41% of the dogs with MPL had concurrent CCLD, and dogs with luxation grade 4 were more likely to have CCLD compared with dogs with luxation grade 1–3.[41]

Three of the breed groups had significantly increased RR of SJD, that is breed groups 2 - pinscher and schnauzer, molossoid and Swiss mountain and cattledogs, 3 - terriers and 9 - companion and toy dogs. The other breed groups had significantly decreased RR. This was anticipated, since the high-risk breed groups included all of the high-risk breeds except for the Chow Chow and the Pomeranian (breed group 5). Several of the SJDs have been identified to have a genetic component, such as PL[25–27,42] and CCLD,[43] but it remains to be elucidated whether this primarily is linked to body size, body constitution or other factors. A genetic component to the aetiology of CCLD and PL is supported by the finding of increased risk of SJD in specific breeds and breed groups,[44] although differentiating a specific genetic risk from inherited aspects of for example conformation and body type as well as environmental factors (for example use, activity) remains challenging.

Females had a small but significant increased RR of SJD compared with males. This is in agreement with previous studies, which have identified that female dogs have higher odds of both CCLD and PL.[4,23,25,27] Neutering has been associated with increased odds of these diseases.[3,4,11] In the present study, it was not possible to evaluate effect of neuter status, as it was not registered in the insurance database.

The yearly incidence of SJD increased dramatically during the 6 year period. The number of DYAR/year did not change substantially from 2011 to 2016, while the number of claims was more than doubled. A similar increase was seen in a study evaluating the prevalence of CCLD in the Veterinary Medical Database (US and Canada) during 1964–2003, where the prevalence increased from 1.81% during the first 10-year period to 4.87 % during the last 10-year period.[11] The authors suggested that this was due to an increased disease recognition by veterinarians, rather than a true increase in disease frequency. Similarly, in the current study, the observed increase in SJD claims over time could be attributed to increased disease recognition, for example due to better diagnostic methods. A shift in treatment recommendations from non-surgical treatment or euthanasia to surgical treatment, or increasing costs for veterinary appointments, could have increased the number of claims that reached the deductible of the insurance. However, an actual increased disease frequency cannot be excluded. A sudden increase of high-risk breeds could have explained the escalating incidence, but this was not apparent in the data (data not shown).

General and specific benefits and limitations of these secondary data must be considered. Insurance data offer a great potential for epidemiologic research, since primary data for research are prohibitively expensive and impractical. The large population renders precise estimates (small CI) which is a benefit, but requires that not only the statistical significance but also the magnitude of the differences is carefully considered. Information is primarily collected for business purposes and may lack variables that would have been of interest for the research project. Bodyweight and neuter status are such variables in the current project, which could act as potential confounders on the association between breed, sex and SJD. Confounding variables can be expected to vary with the actual disease. Therefore, no multivariable analysis was attempted in this explorative study of SJD as a composite diagnosis. As for clinical data, the reporting of claims relies on veterinarians who have different expertise and routines for clinical examinations, diagnostic procedures and writing medical records, although some consistency is imposed by the insurance company. Although unlikely to substantially impact this study, the cost of a veterinary appointment must exceed the deductible of the insurance in order for the claim to be registered, and therefore minor problems that do not progress are not recorded. This large dataset has generally high statistical power, but significant associations in rare breeds will have been found only if their frequency of SJD is very high. In conclusion, the results of the present study represent slightly conservative estimates of incidence but with little or no bias to the RR estimations.

In epidemiological studies, it is important to evaluate whether the study population differs from the target population, which is the population to which the results should be generalised. The study population in the current study consisted of insured dogs. This population may be affected by selection bias, since morbidity and mortality in insured dogs cannot directly be assumed to correctly reflect morbidity and mortality in the uninsured population due to differences in veterinary care.[14] Insured dogs in other countries have, in fact, been shown to have increased odds for both OA, CCLD and PL, compared with uninsured dogs.[3,4,9] This may be due to financial restrictions of owners of uninsured dogs, precluding advanced diagnostic investigations. This argument is supported by one study from Great Britain, which reported that the odds of a dog being insured were significantly higher among those living in less compared to most deprived areas.[45] In contrast to many other countries the majority of the Swedish dog population is insured (77% during 2012), and Agria data reflect approximately 50% of those insured dogs. In addition, breeds have similarities across countries, in general, and there are close genetic links between many dog breeds in Sweden and other European countries.[14] Therefore, the study population is relatively representative, and results from the present study are informative for both the general Swedish dog population and for many breeds outside Sweden.

In conclusion, SJD was common in the insured dog population. Several breeds were identified to be at high or low risk of SJD, and there was a clear distinction between the breeds that accounted for highest proportion of all SJD claimed dogs and the breeds with highest RR of SJD. Some breeds, such as the Rottweiler and Labrador retriever, were primarily affected by CCLD, while others, such as the Chihuahua, were primarily affected by patellar luxation. Others, for example the miniature and toy poodles, Bichon frise and Yorkshire terrier, were affected by both conditions. Female dogs had increased RR compared with male dogs, and there was an increasing incidence during the study period. The demographic factors associated with SJD in the current study may guide veterinarians in their clinical work and educate dog owners about breeds at risk of disease. Further, results can be used to highlight the importance of various SJD and guide future research projects evaluating the aetiopathogenesis of these diseases, with the objective to identify why certain individuals are affected.

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AUTHOR CONTRIBUTIONS

All authors (Karolina Engdahl, Jeanette Hanson, Odd Höglund, Annika Bergström, Brenda Bonnett, Ulf Emanuelson) contributed to the study design. Karolina Engdahl carried out the data analysis under supervision from Ulf Emanuelson, Jeanette Hanson and Brenda Bonnett. Karolina Engdahl wrote the manuscript, with substantial input from the other authors (Jeanette Hanson, Odd Höglund, Annika Bergström, Brenda Bonnett, Ulf Emanuelson). All authors (Karolina Engdahl, Jeanette Hanson, Odd Höglund, Annika Bergström, Brenda Bonnett, Ulf Emanuelson) read and approved the final manuscript.

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SUPPORTING INFORMATION

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

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Table S1. The categorization of the stifle joint diagnoses into 14 categories.

Category	**Diagnosis**
Arthritis	Acute inflammation, stifle joint
Arthritis	Chronic inflammation, stifle joint
Arthritis	Chronic purulent arthritis, stifle joint
Arthritis	Chronic serous arthritis, stifle joint
Arthritis	Infectious/inflammatory changes, stifle joint
Arthritis	Other acute inflammation, stifle joint
Arthritis	Other chronic inflammation, stifle joint
Arthritis	Purulent arthritis, stifle joint
Arthritis	Serous/serous fibrinous arthritis, stifle joint
Arthritis	Specific chronic inflammation, stifle joint
Arthritis	Specific infectious diseases, stifle joint
Arthritis	Specific, acute inflammation, stifle joint
Cruciate ligament rupture	Bilateral cruciate ligament rupture
Cruciate ligament rupture	Cruciate ligament rupture
Degenerative changes	Chronic, deforming osteoarthrosis, stifle joint
Degenerative changes	Degeneration of articular cartilage, stifle joint
Degenerative changes	Degeneration of ligament, stifle joint
Degenerative changes	Degenerative/dystrophic changes, stifle joint
Degenerative changes	Metabolic, nutritional, degenerative/dystrophic changes, stifle joint
Fracture	Complication during fracture healing, patella/fabella
Fracture	Fissure of patella/fabella
Fracture	Fracture of femur involving the stifle joint
Fracture	Fracture of patella/fabella
Fracture	Fracture of patella/fabella, special type
Fracture	Fracture of tibia/fibula involving the stifle joint
Immune-mediated	Arterio-athero-sclerosis changes, patella/fabella
Immune-mediated	Arterio-athero-sclerosis changes, stifle joint
Immune-mediated	Immune-mediated disorders, stifle joint
Immune-mediated	Rheumatoid arthritis, stifle joint
Inflammation, patella/fabella	Acute inflammation, patella/fabella

Inflammation, patella/fabella	Acute periostitis, patella/fabella
Inflammation, patella/fabella	Infectious/inflammatory changes, patella/fabella
Meniscal injury	Bilateral traumatic meniscal injury
Meniscal injury	Non-traumatic meniscal injury
Meniscal injury	Traumatic meniscal injury
Osteochondrosis	Osteochondrosis, femur
Osteochondrosis	Osteochondrosis, femur, with joint mouse
Osteochondrosis	Osteochondrosis, femur, without joint mouse
Osteochondrosis	Osteochondrosis, patella/fabella
Other malformations & growth disorders	Developmental/growth disorder, patella/fabella
Other malformations & growth disorders	Developmental/growth disorder, stifle joint
Other malformations & growth disorders	Malformation, developmental/growth disorder, stifle joint
Other malformations & growth disorders	Malformation, patella/fabella
Other malformations & growth disorders	Other developmental disorder, stifle joint
Pain or unspecified signs, patella/fabella	Changed position, patella/fabella
Pain or unspecified signs, patella/fabella	Malpositioned skeletal parts in patella/fabella
Pain or unspecified signs, patella/fabella	Normal variation/symptom without confirmed cause, patella/fabella
Pain or unspecified signs, patella/fabella	Other changed position, patella/fabella
Pain or unspecified signs, patella/fabella	Patella, fabella
Pain or unspecified signs, patella/fabella	Skeletal tenderness, patella/fabella
Pain or unspecified signs, patella/fabella	Symptoms without confirmed cause, patella/fabella
Pain or unspecified signs, stifle joint	Calcinosis circumscrpita, stifle joint
Pain or unspecified signs, stifle joint	Changed circulation, stifle joint
Pain or unspecified signs, stifle joint	Changed positions in stifle joint
Pain or unspecified signs, stifle joint	Crepitation in stifle joint, without further specification
Pain or unspecified signs, stifle joint	Haemorrhage, stifle joint
Pain or unspecified signs, stifle joint	Hyperextension, stifle joint
Pain or unspecified signs, stifle joint	Idiopathic, unspecific, multifactorial, stifle joint
Pain or unspecified signs, stifle joint	Increased amount of synovia without further specification
Pain or unspecified signs, stifle joint	Increased mobility, stifle joint
Pain or unspecified signs, stifle joint	Joint mouse (not secondary to OCD)
Pain or unspecified signs, stifle joint	Normal variation/symptom without confirmed cause, stifle joint
Pain or unspecified signs, stifle joint	Oedema, stifle joint
Pain or unspecified signs, stifle joint	Pain stifle joint, during extension/flexion

Pain or unspecified signs, stifle joint	Pain stifle joint, during palpation
Pain or unspecified signs, stifle joint	Pain, stifle joint
Pain or unspecified signs, stifle joint	Stiffness, stifle joint
Pain or unspecified signs, stifle joint	Swollen stifle joint, no further specification
Pain or unspecified signs, stifle joint	Symptoms without confirmed cause, stifle joint
Patellar luxation	Bilateral lateral patellar luxation
Patellar luxation	Bilateral medial patellar luxation
Patellar luxation	Bilateral patellar luxation, unspecified
Patellar luxation	Lateral patellar luxation
Patellar luxation	Medial patellar luxation
Patellar luxation	Patellar luxation, unspecified
Traumatic injuries	Collateral ligament rupture
Traumatic injuries	Distorsion, stifle joint
Traumatic injuries	Ligament rupture, stifle joint
Traumatic injuries	Stifle luxation
Traumatic injuries	Subluxation, stifle joint
Traumatic injuries	Trauma, foreign body, changed position, termal injury, patella/fabella
Traumatic injuries	Trauma, foreign body, changed position, termal injury, stifle joint
Traumatic injuries	Traumatic/mechanic injuries, patella/fabella
Traumatic injuries	Traumatic/mechanic injuries, stifle joint
Traumatic injuries	Wound perforating joint capsule, stifle joint
Tumour	Benign tumour in patella/fabella/cartilage, joint included
Tumour	Benign tumour, stifle joint
Tumour	Malign tumour, stifle joint
Tumour	Neoplasia, stifle joint
Tumour	Osteosarcoma, patella/fabella
Tumour	Synovial sarcoma, stifle joint
Tumour	Synovioma, stifle joint
Tumour	Tumour in stifle joint, unspecified

II

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The epidemiology of cruciate ligament rupture in an insured Swedish dog population

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Cruciate ligament rupture (CLR) is a common orthopedic disorder in dogs. The study objectives were to evaluate incidence rate (IR), cause-specific mortality rate (CSMR) and risk factors for CLR in insured dogs. A single cohort study of dogs insured in Agria Pet Insurance in Sweden (2011–2016) was performed. Age at diagnosis, IR, CSMR and relative risk (RR) for CLR was calculated overall and per breed. The cohort included just over 600,000 dogs. The IR of CLR was 23.8 (95% confidence interval, 23.1–24.6) cases per 10,000 DYAR. The breeds with highest RR of CLR were Boerboel and Dogo Canario, while the breeds with lowest RR were Standard Dachshund and Miniature Pinscher. Dogue de Bordeaux had highest RR of euthanasia due to CLR. The median age at veterinary care claim for CLR was 7.1 (range 0.3–16.0) years and 6.6 (0.3–12) years at life insurance settlement. Large and giant breeds were generally diagnosed and euthanized due to CLR at a younger age compared to smaller breeds. The majority of the breeds with increased RR of CLR diagnosis and CLR-related euthanasia were large or giant. A pattern of increasing size and decreasing age at diagnosis/CLR-related euthanasia was observed.

Cranial cruciate ligament disease (CCLD) is among the most common orthopedic disorders in dogs[1], and the most common stifle joint disease requiring veterinary care[2]. Many factors, including anatomical configuration, environment and genetics, are suggested to contribute to development of CCLD, and the complex and likely multifactorial origin of the disease makes it challenging to develop preventive strategies[3–5]. The condition can be treated either surgically or conservatively, and there are over 60 variations of surgical procedures described[6]. The treatment is often costly; it was estimated that the total cost of CCLD treatment in the US during 2003 was 1.32 billion dollars[7]. Rupture of the caudal cruciate ligament with intact cranial cruciate ligament is much more uncommon, and is often caused by trauma[1,8].

The reported prevalence of CCLD varies between 0.56–2.55%[9–11]. However, these prevalence estimates are based on data from veterinary clinics, which may represent a biased proportion of dogs from the general dog population. Population based estimates of disease occurrence are necessary in order to evaluate the impact of CCLD at a population level. Insurance data are feasible for such calculations, given that a sufficient proportion of the dog population is insured. In Sweden, 77% of all dogs were covered by veterinary care insurance during 2012, and during 2016 38% of the dog population was insured in Agria Pet Insurance[12,13]. The Agria Pet Insurance database has been used in epidemiological studies of conditions such as atopic dermatitis, dystocia, epilepsy, and adrenocortical insufficiency[14–17].

Several breeds such as Rottweiler, Labrador Retriever and Newfoundland are reported as predisposed to CCLD, and the disease often affects middle-aged to older dogs with a reported median age of 4.3–7.0 years at presentation[9,11,18,19]. Females and neutered dogs are generally reported as predisposed to the condition[9–11,19,20]. Comorbidities such as hip dysplasia and patellar luxation have been described in dogs with CCLD, but if these comorbidities act as risk factors for CCLD is not fully evaluated[9,21–23].

Even though the long-term treatment results for CCLD generally are reported as successful, the disease frequently results in osteoarthritis and chronic pain, which in severe cases could result in euthanasia[24–26]. There is limited information about euthanasia due to CCLD, but one study reported a cause-specific mortality of 2 cases per 10,000 dog-years at risk (DYAR) in dogs insured in Agria Pet Insurance 1995–2000[27]. A study including Norwegian and Swedish dogs treated for CCLD at two University Animal Hospitals reported that 61 of the 333 included dogs (18.3%) were euthanized for reasons related to CCLD at some point after treatment initiation[22]. The most common reason for CCLD-related euthanasia was persistent lameness from the affected limb. Many

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studies have reported that the risk of CCLD varies with breed, but it is not known if the same applies to the risk of CCLD-related euthanasia.

The objective of the study was to provide population-based estimates of incidence rate, cause-specific mortality rate, and age at diagnosis of cruciate ligament rupture (CLR) for dogs insured in Agria Pet Insurance (Agria Djurförsäkring, Stockholm, Sweden) in Sweden. Additional aims were to investigate whether the affected dogs had claims for other diagnoses prior to the CLR, and if the age at diagnosis and relative risk (RR) of CLR varied with breed. The diagnostic codes of the claims in the Agria Pet Insurance database are based on a hierarchical diagnostic registry developed by the Swedish Association of Veterinary Clinics and Hospitals[28], and do not differentiate between cranial and caudal cruciate ligament rupture. Caudal cruciate ligament rupture has been reported as much more uncommon than CCLD[1], and a recent report shows that damage to the caudal cruciate ligament in dogs with CCLD is common, which suggests a mutual underlying pathogenic mechanism[29]. Thus, the results of the current study will be compared to studies evaluating only CCLD.

Materials and methods

Data. This was a single cohort study comprising data on dogs insured in Agria Pet Insurance in Sweden between January 1, 2011 and December 31, 2016. There were two types of insurances—veterinary care and life. The data collected included information about breed, sex (female/male, but not neuter status), date of enrollment and termination of the insurance, age at start of the observation period and date and diagnostic codes for veterinary care claims and life insurance settlements (if any). The life insurance terminated at 8, 10 or 12 years of age, depending on breed (see supplementary Table 1). The dogs could be enrolled in veterinary care insurance at any age, but in life insurance only before the age of 4 years (for breeds with insurance termination at 8 years) or 6 years (all other breeds). The age at observation start was based on the median age in the population at 1 January, 2011. The breed variable was based on the classification by Federation Cynologique Internationale (FCI) and the Swedish Kennel Club (SKC). Seven breeds were non-approved by both FCI and the SKC; Old English Bulldog, American Bulldog, Boerboel, Pitbull Terrier, Alaskan Husky, Hedehund and Griffon à Poil Laineux/Boulet. All available breeds were included in the analysis.

The deductible of the veterinary care insurance was chosen by the owner at insurance enrollment, and the claims were registered by a clerk at the company if the total cost of all veterinary appointments during rolling 125-days periods exceeded the deductible. In case receipts from several veterinary appointments were submitted at the same time, they were usually registered as separate claims on the same date. Claims for non-traumatic CLR were reimbursed only after a waiting period of 12 months after insurance enrollment in dogs insured after the age of four months. Two diagnostic codes were included in the database search: "Cruciate ligament rupture" and "Cruciate ligament rupture, several joints". Since it was not possible to differentiate between cranial and caudal cruciate ligament rupture in the database, different terminology will be used when the results are compared to results from other studies; CLR for the current study, and CCLD for studies evaluating only CCLD.

The age at diagnosis was based on the first registered veterinary care claim for CLR during the observation period or the date when a life insurance settlement was registered in the database. In addition, all claims for other conditions were extracted and included in the analysis for dogs with veterinary care claims for CLR. There was no information about claims before the start of the observation period, and claims for diseases present before insurance enrollment were not reimbursed. Settlement of life insurance required a certificate from the veterinarian, sometimes in combination with an autopsy depending on the cause of death. Euthanasia and natural death were not distinguished in the database. Dogs were excluded in case of uncertain information about age, sex, breed or date of insurance enrollment (for example dogs with date of insurance enrollment before date of birth etc.).

Analysis. Data analysis was performed in RStudio version 1.2.1335[30]. Continuous variables are presented as median (range) and categorical variables as number (percentage). Wilcoxon rank-sum test was used to compare median age between groups, since the Shapiro–Wilk test showed that the age variable was not normally distributed. Two-sided one sample z test of proportions was used to compare proportions. Dog-years at risk (DYAR) was based on the total insurance duration for each dog during the study period (2011–2016). For incidence calculation, the DYAR in dogs with CLR claims during the study period was based on the time period until the first CRL claim. The incidence rates and cause-specific mortality rates were expressed as the number of dogs with veterinary care claims or life insurance settlements due to CLR per 10,000 DYAR. Relative risk for breed was calculated by dividing the incidence rate/cause-specific mortality rate for the breed by the incidence rate/cause-specific mortality rate of the rest of the population (with the breed excluded). Relative risk for sex was calculated similarly. Confidence intervals (CI) were calculated with the R-package "exactci" (version 1.3-3)[31] based on the Poisson distribution. Bonferroni correction, based on the number of subgroups included in the comparison, was used to adjust for multiple comparisons. P-values < 0.05, after corrections, were considered to indicate statistically significant differences. Breed risks were described using forest plots from the R-package "forestplot" (version 1.9)[32].

Results

The database included just over 600,000 insured dogs, and 649 dogs were eliminated due to the exclusion criteria. The majority of the dogs (61.8%) had both veterinary care and life insurance, while the remaining dogs had only veterinary care insurance (35.5%) or life insurance (2.7%). Descriptive features of the dog population are presented in Table 1.

The overall incidence rate of CLR was 23.8 (95% CI, 23.1–24.6) cases per 10,000 DYAR. In total, 181 breeds had at least one dog with a veterinary care claim for CLR. Of these, 26 breeds had significantly increased risk of CLR, while 18 breeds had significantly decreased risk (that is, RR either significantly higher or lower than 1)

	Insurance	
	Veterinary care	**Life**
Total duration of insurance (years)	> 1.7 million	> 1.1 million
Insurance duration, median (range)*	2.7 y (9.1 w–6.0 y)	2.5 y (9.1 w–6.0 y)
Age at observation start, median (range)	2.4 y (3.4 w–21 y)	1.6 y (3.4 w–12 y)
Sex (%)		
Female	49	50
Male	51	50
Number of dogs with claims for CLR	4167	447
CLR	4142	432
Bilateral CLR	45	15
Age at CLR claim, median (range)**	7.1 y (13.3 w–16 y)	6.6 y (16.3 w–12 y)

Table 1. Descriptive features of dogs insured in Agria Pet Insurance in Sweden, 2011–2016. *Per dog, during 2011–2016. **Age at first CLR claim during 2011–2016 for dogs with veterinary care insurance. *CLR* cruciate ligament rupture, *y* years, *w* weeks.

after Bonferroni correction (Fig. 1, for a full list without Bonferroni correction, see supplementary Table 3). The breeds with highest risk of CLR were Boerboel (RR 11.0, 95% CI, 5.84 – 18.8) and Dogo Canario (RR 7.92, 95% CI, 3.42–15.6) and the breeds with lowest risk were the Standard Dachshund (RR 0.07, 95% CI, 0.03–0.13) and the Miniature Pinscher (RR 0.05, 95% CI, 0.00–0.28).

Female dogs were at increased risk of having a CLR veterinary care claim compared to male dogs (RR 1.13, 95% CI, 1.06–1.20, $p < 0.001$). Of the 4167 dogs with veterinary care claims for CLR, 2762 (66.3%) had a concurrent life insurance. Of these, 466 dogs had a life insurance settlement during the observation period, of which 234 (50.2%) were due to CLR. Median time from CLR veterinary care claim to life insurance settlement due to CLR was 7 days (0–4.25 years). Time from diagnosis of CLR to euthanasia varied with age at diagnosis; it was significantly shorter in dogs diagnosed > 9 years of age, compared to dogs diagnosed < 3 years of age ($p = 0.0086$).

The age at diagnosis and at life insurance settlement due to CLR varied with breed. Breeds with a median age that differed significantly from all other breeds are presented in Table 2. In general, the breeds with significantly lower age at diagnosis were large and giant breeds, while the breeds with significantly higher age at diagnosis were small breeds. The same pattern was seen for the age at euthanasia. The dogs with life insurance settlements due to CLR were significantly younger at time of death/euthanasia, than dogs with life insurance settlement for all other reasons (6.61 (range, 0.31–12.0) years versus 7.53 (0.19–12.83) years, $p < 0.001$).

In total, 2656 of the 4167 (63.7%) dogs with veterinary care claims for CLR had previous claims for other diseases. The frequency and distribution of veterinary care claims by organ system is presented in Table 3, with comparison to claims in veterinary care-insured dogs without CLR. Of the 4167 dogs with CLR, 1542 (37.0%) had previous claims for musculoskeletal disorders and 1093 (26.2%) for dermatologic conditions. The most common diagnoses within these organ systems were joint disease and neoplastic skin disease, which affected 913 (21.9%) and 292 (7.01%) of the dogs with veterinary care claims for CLR, respectively (Tables 4 and 5).

The cause-specific mortality rate was 4.04 (95% CI, 3.67–4.43) deaths per 10,000 DYAR, and 99 breeds had at least one dog with a life insurance settlement due to CLR. There were 7 breeds with significantly increased RR and 1 breed with significantly decreased RR of euthanasia due to CLR after Bonferroni correction (Fig. 2 and supplementary Table 4, which consist a full list without Bonferroni correction). The breeds with highest risk of euthanasia due to CLR were the Dogue de Bordeaux (RR 30.4, 95% CI, 16.5–51.5) and the Cane Corso (RR 12.7, 95% CI, 7.04–21.2), while the breed with lowest risk was the Standard Dachshund (RR 0, 95% CI, 0–0.26). There was no difference in risk of euthanasia due to CLR in females compared to males (RR 1.12, 95% CI, 0.93–1.36, $p = 0.24$). Approximately half of the dogs with life insurance settlements due to CLR (52.3%) had a veterinary care claim for CLR at some point before the life insurance settlement.

Discussion

The current study demonstrated large breed-specific differences in incidence rate, cause-specific mortality rate and age at diagnosis of CLR. The breeds with highest RR of CLR were Boerboel, Dogo Canario, American and English Bulldog, Dogue de Bordeaux, Bullmastiff, Chow Chow, Rottweiler and Cane Corso. Some of these breeds, such as the Rottweiler, English Bulldog and Chow Chow, are commonly reported as predisposed to CCLD in other studies, together with Newfoundland, Boxer, Staffordshire Bull Terrier, American Staffordshire Terrier and Yorkshire Terrier, which all are among the high-risk breeds in the current study[9,11,19]. Several of the identified low-risk breeds, for example the Cocker Spaniel, German Shepherd Dog, Chihuahua, Miniature Schnauzer, Shih Tzu, English Springer Spaniel, Pug and Standard Dachshund, are also reported as low-risk breeds in other studies[11,19,20]. Previous reports about the risk of CCLD for the Labrador Retriever are conflicting; some studies report the Labrador Retriever as a high-risk breed[9,19,20], while others found no increased risk[11,33]. In the current study, the Labrador Retriever had a slightly increased RR of CLR. The difference in results may be due to differences in study design and study populations, or regional differences in disease pattern.

Some of the high-risk breeds in the current study, such as Boerboel and Dogo Canario, have not been previously reported as predisposed to CCLD. These breeds were represented by relatively few individuals in the

Breed	Incidence per 10,000 DYAR (95%CI)	RR (95%CI)
Boerboel	261 (139 - 446)	11.0 (5.84 - 18.8)
Dogo Canario	188 (81.3 - 371)	7.92 (3.42 - 15.6)
American Bulldog	171 (97.5 - 277)	7.18 (4.10 - 11.7)
Dogue de Bordeaux	163 (102 - 247)	6.89 (4.31 - 10.4)
English Bulldog	154 (105 - 217)	6.50 (4.44 - 9.20)
Bullmastiff	153 (97.2 - 230)	6.46 (4.09 - 9.71)
Chow Chow	148 (79.0 - 254)	6.24 (3.32 - 10.7)
Rottweiler	127 (112 - 143)	5.62 (4.93 - 6.37)
Cane Corso	118 (85.7 - 158)	4.99 (3.62 - 6.72)
Cairn Terrier	104 (86.0 - 126)	4.48 (3.67 - 5.41)
Lancashire Heeler	95.9 (58.6 - 148)	4.04 (2.46 - 6.25)
Pumi	95.0 (56.3 - 150)	4.00 (2.37 - 6.32)
Bichon Frise	93.0 (76.0 - 113)	3.98 (3.24 - 4.83)
Staffordshire Bull Terrier	88.3 (72.2 - 107)	3.78 (3.08 - 4.58)
Dobermann	87.0 (61.3 - 120)	3.67 (2.58 - 5.07)
Bolognese	86.1 (53.3 - 132)	3.63 (2.24 - 5.55)
Bernese Mountain Dog	81.0 (63.5 - 102)	3.44 (2.69 - 4.33)
Newfoundland	74.5 (43.4 - 119)	3.13 (1.82 - 5.02)
American Staffordshire Terrier	70.8 (54.8 - 89.9)	3.00 (2.32 - 3.82)
American Cocker Spaniel	67.7 (47.2 - 94.2)	2.86 (1.99 - 3.98)
Boxer	63.9 (48.3 - 83.0)	2.71 (2.04 - 3.52)
Yorkshire Terrier	61.3 (48.6 - 76.1)	2.60 (2.06 - 3.24)
Border Terrier	50.2 (40.8 - 61.1)	2.13 (1.73 - 2.60)
Medium Poodle	45.8 (33.9 - 60.5)	1.93 (1.43 - 2.56)
Bichon Havanais	41.0 (31.5 - 52.5)	1.73 (1.33 - 2.22)
Labrador Retriever	34.6 (30.5 - 39.1)	1.48 (1.30 - 1.68)
German Shepherd Dog	13.4 (10.7 - 16.6)	0.56 (0.44 - 0.69)
Cocker Spaniel	10.4 (6.70 - 15.3)	0.43 (0.28 - 0.64)
Border Collie	10.0 (6.81 - 14.2)	0.42 (0.28 - 0.59)
English Springer Spaniel	9.22 (5.55 - 14.4)	0.38 (0.23 - 0.60)
Drever	7.60 (4.05 - 13.0)	0.32 (0.17 - 0.54)
Cavalier King Charles Spaniel	7.40 (4.63 - 11.2)	0.31 (0.19 - 0.46)
Danish-Swedish Farmdog	6.82 (3.63 - 11.7)	0.28 (0.15 - 0.49)
Rhodesian Ridgeback	6.10 (2.24 - 13.3)	0.25 (0.09 - 0.55)
Shih Tzu	5.91 (2.17 - 12.9)	0.25 (0.09 - 0.54)
Miniature Schnauzer	5.90 (3.37 - 9.58)	0.24 (0.14 - 0.40)
Chihuahua	4.48 (2.65 - 7.08)	0.18 (0.11 - 0.29)
Pug	4.36 (1.60 - 9.50)	0.18 (0.07 - 0.40)
Dalmatian	4.05 (0.83 - 11.8)	0.17 (0.03 - 0.49)
Chinese Crested Dog	3.02 (0.98 - 7.05)	0.13 (0.04 - 0.29)
Norwegian Elkhound Grey	2.87 (0.93 - 6.70)	0.12 (0.04 - 0.28)
Finnish Lapphund	2.70 (0.56 - 7.90)	0.11 (0.02 - 0.33)
Standard Dachshund	1.66 (0.76 - 3.15)	0.07 (0.03 - 0.13)
Miniature Pinscher	1.20 (0.03 - 6.69)	0.05 (0.00 - 0.28)

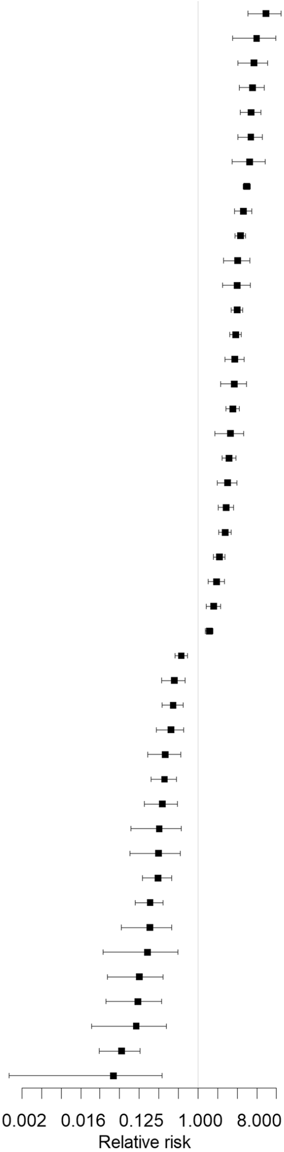

Figure 1. Dog breeds with increased or decreased relative risk (RR) of a veterinary care claim for cruciate ligament rupture (relative to the rest of the population with the breed excluded) in a cohort of dogs insured in Agria Pet Insurance in Sweden (2011–2016). All RRs in the figure were significantly different from 1, after Bonferroni correction based on the number of breeds included in the comparison, n = 339. Note that RR = 0.5 means 2 times decreased risk, RR 0.125 means 8 times decreased risk and so on. *DYAR* dog-years at risk, *CI* confidence interval.

Veterinary care insurance		Life insurance	
Breed	Age* at first CLR claim	Breed	Age at CLR claim
Boerboel	1.98 (1.08–3.98)	Dogo Canario	1.86 (1.81–1.92)
English Bulldog	2.65 (0.79–9.63)	English Bulldog	2.63 (1.93–4.11)
French Bulldog	2.67 (0.25–10.3)	Dogue de Bordeaux**	3.11 (1.48–8.42)
Cane Corso	2.68 (0.56–9.11)	Cane Corso	3.15 (1.08–8.71)
American Staffordshire Terrier	3.56 (0.44–11.5)	Bullmastiff	3.43 (1.30–4.93)
American Bulldog	3.56 (1.44–7.79)	Newfoundland	3.97 (1.25–6.81)
Bullmastiff	3.72 (0.95–6.95)	Rottweiler	4.99 (0.65–9.87)
Dogue de Bordeaux	3.92 (1.01–7.06)	Medium Poodle	8.98 (7.87–11.5)
Staffordshire Bull Terrier	4.75 (0.50–13.6)	Bolognese	9.07 (7.24–9.93)
Boxer	4.92 (0.29–10.4)	Cairn Terrier	9.22 (7.08–10.6)
Rottweiler	5.15 (0.30–11.6)	Miniature and Toy Poodle	9.30 (1.62–10.0)
Jack Russell Terrier	8.44 (0.78–14.5)	Standard Poodle	9.90 (9.72–10.1)
Bichon Frise	8.81 (2.90–14.5)	Soft Coated Wheaten Terrier	10.5 (9.11–12.0)
Border Terrier	9.37 (1.61–13.1)	Border Terrier	10.9 (9.41–11.9)
Miniature and Toy Poodle	9.38 (0.73–13.8)	West Highland White Terrier	11.6 (10.3–11.8)
Cairn Terrier	9.41 (2.18–15.3)		
Pumi	9.48 (7.05–12.2)		
Medium Poodle	9.59 (2.20–13.9)		
West Highland White Terrier	11.1 (5.13–13.2)		
Tibetan Spaniel	11.3 (2.68–12.7)		

Table 2. Median age in years (range) at first veterinary care claim for cruciate ligament rupture (CLR) or at life insurance settlement due to CLR during the observation period (2011–2016) in a cohort of insured Swedish dogs. *The median age at veterinary care claim for CLR in the listed breeds differed significantly from the median age in all other breeds after Bonferroni correction (based on the number of breeds included in the comparison, n = 181). For a full list of breeds with significantly higher/lower median age at veterinary care claim without Bonferroni correction, see supplementary Table 2. **The only breed with median age at CLR life insurance settlement that differed significantly from the median age of all other breeds, after Bonferroni correction (based on the number of breeds included in the comparison, n = 99). The other listed breeds had a median age at life claim that differed significantly from the median of all other breeds, without Bonferroni correction.

Organ system	% of dogs with CLR**	% of dogs without CLR***
Musculoskeletal*	37.0	10.3
Dermatologic*	26.2	17.7
Gastrointestinal*	17.1	15.3
Other (general/unspecific)*	13.5	11.2
Urogenital*	11.8	10.3
Opthalmic*	5.40	4.19
Respiratory	3.53	3.27
Neurologic	2.16	2.02
Hepatic*	2.06	1.43
Endocrine	1.54	1.08
Cardiovascular	1.51	1.62
Hematopoietic	1.10	1.31

Table 3. Previous diagnoses by organ system in dogs with and without cruciate ligament rupture (CLR), in a cohort of dogs insured in Agria Pet Insurance (2011–2016). *The proportion of dogs with diagnoses in these organ systems was significantly higher in dogs with CLR, after Bonferroni correction based on the number of organ systems, n = 12. **In total 4167 dogs with veterinary care claims for CLR. ***All dogs with veterinary care insurance, except for the dogs with CLR claims.

insured dog population, but increased in popularity during the observation period (based on increasing DYAR/year, data not shown). It is possible that these breeds were too uncommon to be identified as high-risk breeds in older studies, and that more recent studies, but with smaller study populations, had too low power to identify

Category	% of dogs with CLR*
Joint disease	21.9
Stifle	15.6
Pain/signs without confirmed cause	8.18
Degenerative changes	3.14
Arthritis	2.30
Patellar luxation	2.14
Meniscal injury	0.79
Traumatic injuries	0.70
Osteochondrosis	0.22
Fracture	0.02
Neoplastic disease	0.02
Hip	*2.93*
Hip dysplasia	0.84
Elbow	2.26
Degenerative changes	0.98
Phalanges	1.30
Degenerative changes	0.26
Several (unspecified) joints	1.13
Degenerative changes	0.34
Shoulder	*0.79*
Osteochondrosis	0.17
Carpus	0.74
Traumatic injuries	0.24
Tarsus	0.55
Traumatic injuries	0.12
Lameness/stiffness (unspecified)	18.1
Back/vertebrae	3.84
Spondylosis	0.82
Other	2.40
Fracture/fissure	0.89
Muscle/tendon/bursa	1.44
Traumatic injuries	0.41

Table 4. Previous musculoskeletal diagnoses in dogs with veterinary care claims for cruciate ligament rupture (CLR) in Agria Pet insurance (2011–2016). *In total 4167 dogs with veterinary care claims for CLR. All subcategories for stifle joint diagnoses are presented. For all other categories the most specific subcategory is presented, even though pain/signs without confirmed cause was generally the most common subcategory.

Category	% of dogs with CLR*
Neoplastic disease	7.01
Dermatitis	6.77
Ear disease	6.29
Traumatic injury	5.47
Claw disease	3.79
Allergic disease	2.78
Pruritus	2.76
Other	1.82
Parasitic infection	0.55
Alopecia	0.34
Seborrhoea	0.10
Autoimmune disease	0.07

Table 5. Previous dermatologic diagnoses in dogs with veterinary care claims for cruciate ligament rupture (CLR) in Agria Pet insurance (2011–2016). *In total 4167 dogs with veterinary care claims for CLR.

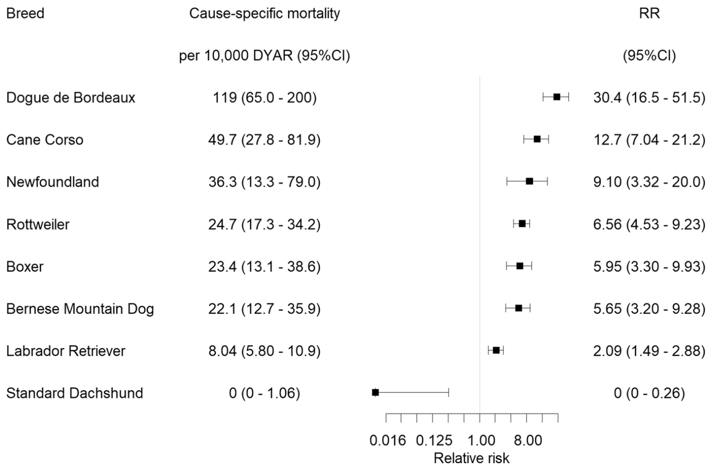

Figure 2. The breeds with increased or decreased relative risk (RR) of death/euthanasia due to cruciate ligament rupture (relative to the rest of the population with the breed excluded) in a cohort of dogs insured in Agria Pet Insurance in Sweden during 2011–2016. All RRs in the figure were significantly different from 1, after Bonferroni correction based on the number of breeds included in the comparison, n = 335. Note that RR = 0.5 means 2 times decreased risk, RR 0.125 means 8 times decreased risk and so on. A fudge factor of 0.01 was added to the RR of Standard Dachshund in order to present the RR on the log-scaled x axis. *DYAR* dog-years at risk, *CI* confidence interval.

these breeds as high-risk. Our findings may also be a result of regional differences in disease pattern, or an actual increase in CLR incidence within these breeds, but our data was not sufficient to investigate such time trends.

The majority of the breeds with highest RR of CLR were large or giant breeds, even though several small breeds such as Bichon Frise, Bolognese and Yorkshire Terrier were among the high-risk breeds. The breeds with low risk of CLR also varied in size from small to large, but the giant breeds were only represented among the high-risk breeds. This indicates that other factors than body size contribute to the development of CCLD, but that giant dogs may be at higher risk compared to dogs of smaller sizes. The fact that certain breeds have increased risk of CLR, irrespective of size, suggests a genetic component to the etiology of the disease, which already has been shown for CCLD in the Newfoundland and the Labrador Retriever[4,34]. The same pattern was seen among the dogs with increased risk of euthanasia due to CLR, where all of the high-risk breeds were large or giant. Increasing body weight has been associated with higher risk of euthanasia due to CCLD[22]. This association may be explained by several factors. For example, the risk for postoperative complications after surgical treatment of CCLD increase with increasing body weight[35–41], and such complications could potentially result in euthanasia in severe cases. In addition, the recovery period after CCLD in a large, heavy dog may be challenging for the owners, as the dog may need to be carried up stairs etc., which can be difficult given the dog's weight. This could also contribute to a decision of euthanasia.

Female dogs were at increased risk of CLR compared to male dogs in the current study, which is supported by previous reports[10,19]. However, many studies report increased risk of CCLD in neutered dogs compared to entire[9,11,20]. The effect of neutering could not be evaluated in the current study, due to lack of information about neuter status in the insurance database. In a survey of the Swedish dog population performed > 20 years ago, only 7.2% of the female dogs and 3.7% of the male dogs were neutered[42]. A more recent study conducted during the study period (2012) concluded that 22.3% (± 4.8%) of the dogs were neutered, with no separation of female/male dogs[12]. Neuter status could potentially have a confounding effect on the association between sex and CLR, if females were neutered to a higher extent than males in the study population.

The median age at diagnosis of CLR was 7.1 years, which is largely in accordance with previous studies[11,18]. There were large breed-specific differences in age at diagnosis; the majority of the breeds with significantly lower age at diagnosis were large or giant, while the majority of the breeds with significantly higher age at diagnosis were small. Information about age at CLR diagnosis by breed is limited in the literature, but a pattern of increasing weight and decreasing age at diagnosis has been described[19,20]. Rottweilers have been reported as younger than other breeds at time of presentation[18]. In addition, several of the breeds with a significantly lower age at diagnosis in the current study (English Bulldog, American Staffordshire Terrier, and Rottweiler) were reported as predisposed to CCLD in a study investigating breed as a risk factor for the CCLD in dogs under two years of age[20]. The age at euthanasia due to CLR showed a similar pattern of increasing size of the breed and decreasing age at euthanasia. Larger dogs generally have a shorter lifespan than smaller, since increasing body weight is negatively correlated with longevity[43]. Thus, a large breed dog may be perceived as "old" at a younger age compared to a smaller dog, which may affect the treatment recommendation by the examining veterinarian and the owner's decision of euthanasia. However, this was probably not the main reason for euthanasia, since the median age at time of euthanasia in several of the large and giant breeds was below four years. Further studies on the connection between age, breed and CLR are warranted.

About 2/3 of the dogs with veterinary care insurance claims for CLR had previous claims for other diseases. Almost 16% had claims for stifle joint disease, and the most common diagnoses were related to pain/signs without confirmed cause, degenerative joint disease and arthritis. It is likely that some of these diagnoses were in fact undiagnosed CCLD, as the cranial drawer test used to diagnose CCLD can be negative in a conscious dog despite a ruptured ligament[44]. Another explanation is that the CCLD is the result of a chronic degenerative process, which may have been a reason for the preceding visits[29,45]. Some diagnoses, i.e. within the musculoskeletal, dermatologic, gastrointestinal, urogenital, ophthalmic and hepatic organ system as well as other, general diagnoses affecting the whole body (such as fatigue), were more common in dogs with CLR compared to dogs without CLR. It is possible that some of these disorders or their associated treatments predisposed to CLR. For example, glucocorticoids are commonly prescribed for long-term treatment of conditions such as atopic dermatitis, and it is known that ligament rupture is a clinical manifestation of hyperadrenocorticism in dogs[46–48]. It is also possible that these diagnoses share common risk factors with CLR. For example, large or giant breeds are reported as more likely to develop both HD, osteoarthritis and CCLD[9,49]. Causal inference between previous diagnoses and the subsequent CLR cannot be drawn, due to the retrospective nature of the study. Despite this, it is important to know that many dogs with CLR had previous or concurrent comorbidities at time of diagnosis. These comorbidities could affect the prognosis for returning to adequate function and mobility, and thus affect the recommendation/decision of treatment by the examining veterinarian and the owner.

There is limited information about cause-specific mortality of CLR in the literature. Even though one should be cautious with direct comparisons between studies, the cause-specific mortality rate of 4.04 (95% CI, 3.67–4.43) deaths per 10,000 DYAR in the current study was higher than the 2 deaths per 10,000 DYAR reported in a study of mortality in the Agria Pet Insurance database 1995–2000[27]. One possible explanation for the increased mortality is increasing veterinary tariffs and the development of advanced surgical treatment options for CCLD. This causes an increased financial burden on the animal owner, who may have chosen euthanasia over a high cost treatment to a higher extent during the study period than > 20 years ago. Of the dogs with CLR life insurance settlements, only 53.1% had a previous veterinary care claim for CLR. It is possible that the dogs without a previous veterinary care claim for CLR had gone through a nonsurgical treatment of the CLR with costs not reaching the deductible of the insurance, since nonsurgical treatment of CLR generally is less costly than surgical treatment[7]. Another possible explanation is that some of the dogs had a CLR veterinary care claim before the start of the observation period. Still, it is likely that some dogs were euthanized at time of CLR diagnosis. Over 50% of the dogs that had a veterinary care claim for CLR and a subsequent life insurance settlement were euthanized due to CLR. The median time from CLR diagnosis to CLR-related euthanasia was 7 days. Some dogs were euthanized at the day of CLR diagnosis, while the maximum time between diagnosis and euthanasia was 4.25 years. The fact that some dogs had several weeks or years between diagnosis and euthanasia may imply that treatment failures occur, and result in euthanasia.

Although insurance data are valuable for epidemiology research, some limitations should be mentioned. Agria Pet Insurance database was validated against practice records > 20 years ago[50]. The validation showed excellent agreement for sex and breed but fair agreement for birth date, with a tendency of better agreement for clinics with computerized medical records. Since computerized medical records are used in the majority of Swedish clinics today, the current agreement is most likely better. The dataset generally has high statistical power, but significant associations in breeds represented by few individuals will have been found only if the CCLD incidence of the breed is very high. Even though the dataset is large, it is important to consider the precision of the estimates when the results are interpreted, which can be done by evaluating the width of the confidence intervals.

The reporting of claims relies on the examining veterinarians, who all have different routines for clinical examinations and diagnostic procedures. There is a risk that some of the dogs with CLR were reported under more unspecific diagnostic codes, such as "Lameness, without further specification". Thus, the incidence rate and cause-specific mortality rate of CLR are probably slightly underestimated. There is also a risk that age at life insurance settlement is underestimated, if dogs were euthanized due to CLR after termination of the life insurance. Increasing bodyweight within breed has been associated with increased odds of CCLD[11], but could not be evaluated in the current study due to lack of information in the database.

Even though there was a separate diagnostic code for bilateral cruciate ligament rupture, it was rarely used. One study of Labrador Retrievers with CCLD reported a frequency of bilateral rupture at initial presentation of 10.6%, and that subsequent rupture occurred in almost 50% of the dogs[51]. In another study, 54% of the dogs developed contralateral CCLD[52]. It is likely that the code "Cruciate ligament rupture" was used for dogs with bilateral rupture in the current study, especially in case of subsequent rupture. Consequently, the true occurrence of bilateral CLR was probably higher than reported. Contralateral CLR has been shown to affect the decision of euthanasia in dogs with CCLD[22]. Thus, there is a risk that bilateral rupture had a confounding effect on the association between breed and mortality due to CLR, if some breeds were affected by bilateral rupture to a higher extent than others.

Morbidity and mortality of insured dogs may not reflect mortality and morbidity in uninsured animals[53]. For example, a study that evaluated CCLD in dogs attending primary-care practices in England reported increased odds of a diagnosis in insured dogs, compared to in uninsured[11]. It is not known if the same pattern exists in dogs insured in Sweden. However, the results of our study are probably representative for the majority of the Swedish dog population due to the high insurance coverage, although a selection bias in the choice of insurance company may exist.

Conclusion

In conclusion, CLR affected more than 4000 dogs in the population, with an incidence of 23.8 (95% CI, 23.1–24.6) cases per 10,000 DYAR. Although dogs of all sizes were affected, the majority of the breeds with increased RR of CLR were large or giant. Large and giant breeds also had an increased risk of euthanasia due to CLR, and were generally diagnosed and euthanized due to CLR at a younger age compared to smaller breeds. Demographic factors associated with CLR provide guidance for veterinarians in their clinical work, and may educate breeders and dog owners about breeds at risk of disease. In addition, the results may guide studies investigating the aetiopathogenesis of CLR. Given the identified breed predispositions, which likely has a genetic component, breeds reforms may be warranted in the future to lower the incidence of CLR.

Data availability

The data analyzed in the current study are not publicly available due to a non-disclosure agreement with Agria Pet Insurance.

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Author contributions

All authors contributed to the study design. K.E. analyzed the data under supervision of U.E. and J.H. K.E. was the major contributor to the manuscript, with substantial input from the other authors (U.E., J.H., A.B., O.H.). All authors read and approved the final version of the manuscript (K.E., U.E., J.H., A.B., O.H.).

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Additional information

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The epidemiology of cruciate ligament rupture in an insured Swedish dog population

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Supplementary table 1. Age at termination of life insurance by breed, for dogs insured in Agria Pet Insurance (2011-2016)

Age group 12	Bichon Havanais, Border Terrier, Cairn Terrier, Chihuahua, Chinese Crested, Miniature Schnauzer, Finnish Lapphund, Finnish Spitz, Fox Terrier, Islandic Sheepdog, Jack Russel Terrier, Lhasa Apso, Poodle (toy, miniature, medium), Münsterländer, Norrbottenspets, Norwegian Buhund, Papillon, Phalene, Schnauzer, Shih Tzu, Soft Coated Wheaten Terrier, Tibetan Spaniel, Tibetan Terrier, Västgötaspets, Welsh Springer Spaniel, West Highland White Terrier, Whippet
Age group 10	All other breeds
Age group 8	Berner Sennen, Grand Danois, Irish Wolfhound, Leonberger, Newfoundland, Pyrenean Mountain Dog, Neapolitan Mastiff, St. Bernard

Supplementary table 2. Median age at first CLR veterinary care claim during the observation period (2011-2016) in a cohort of insured Swedish dogs, for breeds with median age that differed significantly from the median age of all other breeds ($p < 0.05$).

Breed	Median age
Salukis	1.45
Boerboel*	1.98
Bull Terrier	2.42
Dogo Canario	2.43
Leonberger	2.52
English Bulldog*	2.65
French Bulldog*	2.67
Cane Corso*	2.68
St. Bernhards	3.39
American Bulldog*	3.56
American Staffordshire Terrier	3.56
Bullmastiff*	3.72
Dogue de Bordeaux*	3.92
Chow Chow	3.97
English Mastiff	4.22
Newfoundland	4.61
Hovawart	4.68
Staffordshire Bull Terrier*	4.75
Boxer*	4.92
Great Dane	5.15
Rottweiler*	5.15
Dobermann	5.26
Swedish Elkhound	5.74
German Shepherd Dog	6.11
American Cocker Spaniel	7.79
Yorkshire Terrier	7.88
Bichon Havanais	8.00
Jack Russell Terrier*	8.44
Bichon Frise*	8.81
Cavalier King Charles Spaniel	8.89
Fox Terriers	9.00
Beagle	9.11
Coton de Tuléar	9.14
Border Terrier*	9.37
Poodle Miniature & Toy*	9.38
Cairn Terrier*	9.41
Pumi*	9.48
Poodle Medium*	9.59
Norwich Terrier	9.72
Stabyhound	9.76
Japanese Spitz	9.82
Danish-Swedish Farmdog	10.2
Papillon	10.3
Dachshunds Standard	10.3
Shiba Inu	10.4
Münsterländer Small	11.0

West Highland White Terrier*	11.1
Tibetan Spaniel*	11.3
Parson Russell Terrier	11.9
Schipperke	12.2

*significanly older/younger after Bonferroni correction

Supplementary table 3. Breeds with increased or decreased relative risk of a veterinary care claim for cruciate ligament rupture (relative to the rest of the population with the breed excluded) in a cohort of dogs insured in Agria Pet Insurance in Sweden during 2011-2016. All RRs were significantly different from 1 ($p < 0.05$).

Breed	Relative risk (95% CI)
Fila Brasileiro	26.9 (5.55 - 78.7)
Berger de Picardie	19.9 (4.11 - 58.3)
Neapolitan Mastiff	15.0 (1.82 - 54.2)
Perro de Presa Mallorquin/ca de Bo	13.0 (1.57 - 46.9)
Boerboel*	11.0 (5.84 - 18.8)
Entlebucher Sennenhund	8.71 (1.79 - 25.5)
Dogo Canario*	7.92 (3.42 - 15.6)
American Bulldog*	7.18 (4.10 - 11.7)
Dogue de Bordeaux*	6.89 (4.31 - 10.4)
Caucasian Shepherd Dog	6.55 (1.78 - 16.8)
English Bulldog*	6.50 (4.44 - 9.20)
Bullmastiff*	6.46 (4.09 - 9.71)
English Mastiff	6.33 (2.05 - 14.8)
Chow Chow*	6.24 (3.32 - 10.7)
Rottweiler*	5.62 (4.93 - 6.37)
Cane Corso*	4.99 (3.62 - 6.72)
Cairn Terrier*	4.48 (3.67 - 5.41)
American Akita	4.05 (2.02 - 7.25)
Lancashire Heeler*	4.04 (2.46 - 6.25)
Pumi*	4.00 (2.37 - 6.32)
Bichon Frise*	3.98 (3.24 - 4.83)
Staffordshire Bull Terrier*	3.78 (3.08 - 4.58)
Dobermann*	3.67 (2.58 - 5.07)
Bolognese*	3.63 (2.24 - 5.55)
Bernese Mountain Dog*	3.44 (2.69 - 4.33)
Newfoundland*	3.13 (1.82 - 5.02)
American Staffordshire Terrier*	3.00 (2.32 - 3.82)
American Cocker Spaniel*	2.86 (1.99 - 3.98)
Boxer*	2.71 (2.04 - 3.52)
Yorkshire Terrier*	2.60 (2.06 - 3.24)
Swedish Lapphund	2.47 (1.13 - 4.69)
Great Pyrenees	2.41 (1.10 - 4.57)
Border Terrier*	2.13 (1.73 - 2.60)
Poodle Medium*	1.93 (1.43 - 2.56)
Bichon Havanais*	1.73 (1.33 - 2.22)
Beagle	1.60 (1.08 - 2.27)
Labrador Retriever*	1.48 (1.30 - 1.68)
Jack Russell Terrier	1.31 (1.09 - 1.55)
Swedish Elkhound	0.63 (0.48 - 0.81)
Soft Coated Wheaten Terrier	0.56 (0.33 - 0.89)
Wachtelhund	0.56 (0.35 - 0.86)
German Shepherd Dog*	0.56 (0.44 - 0.69)
Lagotto Romagnolo	0.54 (0.26 - 0.99)
Shetland Sheepdog	0.54 (0.35 - 0.79)
Papillon	0.51 (0.29 - 0.83)

Whippet	0.51 (0.25 - 0.91)
Parson Russell Terrier	0.47 (0.20 - 0.93)
Poodle Standard	0.45 (0.26 - 0.73)
Cocker Spaniel*	0.43 (0.28 - 0.64)
Petit Basset Griffon Vendéen	0.42 (0.17 - 0.86)
Border Collie*	0.42 (0.28 - 0.59)
English Springer Spaniel*	0.38 (0.23 - 0.60)
Siberian Husky	0.36 (0.13 - 0.79)
Collie Rough	0.36 (0.17 - 0.65)
Drever*	0.32 (0.17 - 0.54)
Cavalier King Charles Spaniel*	0.31 (0.19 - 0.46)
Welsh Springer Spaniel	0.29 (0.11 - 0.64)
Bearded Collie	0.28 (0.08 - 0.73)
Danish-Swedish Farmdog*	0.28 (0.15 - 0.49)
Rhodesian Ridgeback*	0.25 (0.09 - 0.55)
Shih Tzu*	0.25 (0.09 - 0.54)
Schnauzers Miniature*	0.24 (0.14 - 0.40)
German Hunting Terrier	0.19 (0.02 - 0.69)
Chihuahua*	0.18 (0.11 - 0.29)
Pug*	0.18 (0.07 - 0.40)
Dalmatian*	0.17 (0.03 - 0.49)
Münsterländer Small	0.16 (0.02 - 0.59)
Finnish Spitz	0.15 (0.02 - 0.54)
Chinese Crested*	0.13 (0.04 - 0.29)
Norwegian Elkhound Grey*	0.12 (0.04 - 0.28)
Finnish Lapphund*	0.11 (0.02 - 0.33)
Tervueren	0.10 (0.00 - 0.56)
Irish Red Setter	0.10 (0.00 - 0.56)
Dachshund Miniature	0.09 (0.00 - 0.52)
Dachshund Standard*	0.07 (0.03 - 0.13)
Miniature Pinscher*	0.05 (0.00 - 0.28)
Basenji	0 (0 - 0.62)
Basset Hound	0 (0 - 0.89)
Briard	0 (0 - 0.66)
Collie Smooth	0 (0 - 0.82)
German Spitz Medium	0 (0 - 0.62)
Greyhound	0 (0 - 0.57)
Italian Greyhound	0 (0 - 0.63)
Norrbottenspitz	0 (0 - 0.47)

*Increased or decreased RR (relative to the rest of the population with the breed excluded) after Bonferroni correction

CI confidence interval.

Supplementary table 4. The breeds with increased or decreased RR of death/euthanasia due to cruciate ligament rupture (relative to the rest of the population with the breed excluded) in a cohort of dogs insured in Agria Pet Insurance in Sweden during 2011-2016. All RRs were significantly different from 1 ($p < 0.05$)

Breed	Relative risk (95% CI)
Neapolitan Mastiff	66.8 (8.07 - 242.9)
Perro de Presa Mallorquin/ca	44.2 (1.12 - 247.6)
Dogue de Bordeaux*	30.4 (16.5 - 51.5)
Tibetan Mastiff	15.9 (1.92 - 57.9)
Dogo Canario	15.1 (1.83 - 54.9)
American Bulldog	14.6 (3.00 - 43.0)
Chow Chow	14.6 (3.96 - 37.7)
Cane Corso*	12.7 (7.04 - 21.2)
Bullmastiff	9.73 (3.14 - 22.9)
Great Pyrenees	9.48 (2.57 - 24.5)
Newfoundland*	9.10 (3.32 - 20.0)
St. Bernhard	7.25 (1.49 - 21.3)
English Bulldog	7.23 (2.34 - 17.0)
Bolognese	7.10 (2.29 - 16.7)
Rottweiler*	6.56 (4.53 - 9.23)
Boxer*	5.95 (3.30 - 9.93)
Bernese Mountain Dog	5.65 (3.20 - 9.28)
Labrador Retriever*	2.09 (1.49 - 2.88)
Norwegian Elkhound Grey	0.18 (0.00 - 0.99)
Cavalier King Charles Spaniel	0.11 (0.00 - 0.59)
Chihuahua	0.09 (0.00 - 0.50)
Chinese Crested	0 (0 - 0.75)
Dachshund Standard*	0 (0 - 0.26)
English Springer Spaniel	0 (0 - 0.68)

*Increased or decreased RR (relative to the rest of the population with the breed excluded) after Bonferroni correction

CI confidence interval.

III

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Risk factors for severe postoperative complications in dogs with cranial cruciate ligament disease – A survival analysis

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ABSTRACT

Objective: To analyze the effect of surgical technique and other risk factors on severe postoperative complications in dogs with cranial cruciate ligament disease (CCLD).

Materials and Methods: A cohort study of 255 dogs (287 stifles) surgically treated for CCLD at two veterinary university hospitals (2011–2016) was performed. The electronic medical records were reviewed and dog owners and referring veterinarians contacted for additional information. The complications were classified as minor, major and catastrophic, where major and catastrophic were considered severe. A multivariable Cox proportional hazards model was applied to assess risk factors for severe postoperative complications.

Results: Three surgical techniques were used; lateral fabellotibial suture (LFS, 141 stifles), tibial plateau leveling osteotomy (TPLO, 77 stifles) and tibial tuberosity advancement (TTA, 69 stifles). The most common severe postoperative complications were surgical site infections or complications related to the surgical implant. Severe postoperative complications occurred in 31 % of the stifles treated with TPLO, 22 % of the stifles treated with LFS and 25 % of the stifles treated with TTA. The multivariable Cox proportional hazards model identified surgical technique ($p = 0.0258$) as a risk factor for severe postoperative complications; TPLO had a significantly lower hazard than LFS (hazard ratio (HR) = 0.37, $p = 0.007$) when controlling for body weight and age, which also were identified as risk factors (HR = 1.05, $p < 0.001$ and HR = 0.91, $p = 0.047$, respectively).

Conclusion and Clinical relevance: Although TPLO procedures had the highest occurrence of severe postoperative complications, the hazard was lower than for LFS after adjusting for body weight and age. This implies that it is important to consider potential effect-modifiers when comparing postoperative complications after CCLD surgery.

1. Introduction

Cranial cruciate ligament disease (CCLD) is one of the most common orthopedic conditions in dogs (Johnson et al., 1994). There are more than 60 variations of surgical procedures described for treatment of CCLD, including extracapsular stabilization techniques such as lateral fabellotibial suture (LFS) and osteotomy techniques such as tibial plateau leveling osteotomy (TPLO) and tibial tuberosity advancement (TTA) (Bergh et al., 2014). Both TPLO and TTA aim to neutralize the tibiofemoral shear force in the stifle joint with ruptured cranial cruciate ligament (CCL) by altering the geometry of the stifle, without replacing the ligament (Slocum and Slocum, 1993; Montavon et al., 2002). The LFS technique inhibits the cranial drawer motion, i.e. the cranial tibial subluxation that occurs when the cranial cruciate ligament is deficient, by placing a stabilizing, extracapsular suture (Schulz, 2012). Cranial cruciate ligament disease frequently results in chronic pain, and osteoarthritis progresses in the affected joint despite surgical treatment (Lazar et al., 2005; Au et al., 2010; Christopher et al., 2013; Mölsä et al., 2013).

The surgical techniques are associated with a variety of postoperative complications, ranging in severity from mild to catastrophic

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(Casale and McCarthy, 2009; Christopher et al., 2013). Complications can both delay the healing process, result in additional costs for the animal owner, increase patient morbidity, and cause greater postoperative pain (Nicoll et al., 2014). Some postoperative complications, such as surgical site infections (SSIs), may occur after any surgical procedure (Eugster et al., 2004). Others are procedure specific, such as tibial tuberosity fractures after TPLO and TTA, fibular fractures after TPLO, and complications associated with the suture material after LFS (Casale and McCarthy, 2009; Dymond et al., 2010; Bergh and Peirone, 2012). The reported complication frequency after CCLD surgery is typically between 11 and 36 % and several preventive or risk factors for complications have been evaluated, such as body weight, age, experience of the surgeon and the use of postoperative antibiotics (Pacchiana et al., 2003; Lafaver et al., 2007; Casale and McCarthy, 2009; Tuttle and Manley, 2009; Fitzpatrick and Solano, 2010; Steinberg et al., 2011; Taylor et al., 2011; Wolf et al., 2012; Christopher et al., 2013; Gordon-Evans et al., 2013; Coletti et al., 2014; Garnett and Daye, 2014; Yap et al., 2015; Hans et al., 2017; Lopez et al., 2018). However, comparing complication severity, occurrence and risk factors between studies can be challenging due to the heterogeneity in classification of the complications, study designs, study populations and differences in case follow-up. As a measure to facilitate comparison of complications between studies, a standardized definition with criteria for documentation of complications in clinical orthopedic studies in veterinary medicine was proposed by Cook et al. (2010), classifying complications as catastrophic, major or minor depending on their severity.

Although many studies have evaluated postoperative complications after surgical treatment of CCLD, comparisons of complication frequency for more than two surgical techniques are sparse (Christopher et al., 2013; Mölsä et al., 2014). Typically, only dogs with complete data are included (per-protocol analysis) and logistic regression models, considering complications as either present or absent, are applied for data analysis. Survival analysis is an alternative to the classic regression techniques, and is superior in handling incomplete information, since the individuals that are lost to follow-up are included as long as they are observed. Survival analysis is rarely used in small animal orthopedics, although common in human orthopedic studies (Khan, 2017).

Identification of risk factors for the development of complications allows for interventions in order to decrease postoperative morbidity, and is important for veterinarians and dog owners facing a decision of CCLD treatment. Thus, the objective of the current study was to evaluate the effect of surgical technique and other risk factors on development of severe postoperative complications in dogs with CCLD, treated by either TPLO, TTA or LFS. The hypothesis was that surgical technique as well as other factors such as body weight and age of the dogs would influence the hazard of severe postoperative complications.

2. Materials and methods

2.1. Study design

A historical cohort study of dogs with CCLD surgically treated with either TPLO, TTA or LFS at two veterinary university hospitals (VHs, Hospital 1: University Animal Hospital, Norwegian University of Life Sciences and Hospital 2: University Animal Hospital, Swedish University of Agricultural Sciences) between 1st January 2011 and 31st December 2016 was performed.

2.2. Inclusion/exclusion criteria

Inclusion criteria was a diagnosis of CCLD confirmed by the cranial drawer test, a positive tibial thrust and/or inspection of the ruptured ligament by arthroscopy or arthrotomy. The medical records were reviewed between 1st January and 31st August 2018, and information including age, sex, breed, body weight, concurrent or subsequent contralateral CCLD, lameness duration prior to diagnosis, clinical examination findings, surgical technique, date of treatment and postoperative complications was recorded. If information was lacking in the medical records, telephone interviews were performed with dog owners or referring veterinarians between 1st August and 15th October, 2018. The dogs were followed until the date of the telephone interview with the dog owner, or to the last recorded visit in the medical record if the owner could not be reached. Neuter status was not consistently registered in the medical records and thus not recorded.

Exclusion criteria were missing information about lameness prior to treatment initiation, concurrent rupture of the collateral ligament, less than 14 days follow-up time, treatment of the contralateral CCL prior to the study period and dogs surgically treated with other techniques than LFS, TPLO and TTA. In addition, dogs with only mild fraying of the cranial cruciate ligament (assessed during visual inspection of the ligament) were excluded. These dogs had concurrent stifle joint disease (such as osteochondrosis), which was considered the main cause of the clinical signs by the responsible surgeon.

2.3. Classification of complications

The complications were classified as catastrophic, major or minor (Cook et al., 2010). According to the classification, a catastrophic complication resulted in unacceptable function/euthanasia/death, a major complication required further surgical or medical treatment and a minor complication resolved without further treatment. However, a few modifications were done; complications resolved by topical antibiotics or a few days of analgesic treatment were classified as minor instead of major. As the aim of the study was to explore severe postoperative complications, all major and catastrophic complications were combined into one category. Clinical signs from the gastrointestinal tract were not registered as complications.

Surgical site infections were not classified as deep/superficial according to the general definition (Horan et al., 2008), due to lack of information in the medical records (i.e. lack of bacterial samples from implants/bones when deep SSIs were suspected). A SSI was registered if the examining veterinarian suspected a SSI, regardless of the result of the bacterial samples (in case sampling was performed). Reoperations and joint lavage due to suspected postoperative septic arthritis were recorded. Surgical site infection or septic arthritis after reoperation were recorded as complications if the reoperation was <1 month after the index surgery.

2.4. Risk factors

Treatment was set as the main exposure variable and separated into three categories; LFS, TPLO and TTA. Dogs with concurrent or subsequent contralateral CCLD were included as two cases if both stifles were surgically treated at the VHs during the study period. A causal diagram for identification of risk factors, intervening and confounding variables for severe postoperative complications was created. In addition, a coefficient change of >20 %, with a potential confounder included in the statistical model was taken to indicate confounding (Dohoo et al., 2009). The following variables from the causal diagram were considered for inclusion in the statistical model: age, arthrotomy/arthroscopy, body weight, breed, concurrent medical and orthopedic comorbidities, duration of anesthesia, duration of lameness prior to treatment (<2 or $\geq$ 2 weeks), experience of the surgeon (experienced surgeon, resident, board-certified), hospital, insurance status, overweight (body condition score $>5/9$, $>3/5$ or judged as overweight by the examining veterinarian), sex, surgical technique and year of treatment (to control for unmeasured factors at the hospitals that may have changed during the study period, such as pre-operative routines). Breed was included as a categorical variable, with separate levels for breeds represented by >10 cases. The variable for orthopedic comorbidity included subcategories for common diseases causing hindlimb lameness; patellar luxation, stifle osteochondrosis and hip dysplasia as well as a category for other orthopedic conditions. The remaining variables in the causal diagram (postoperative antibiotic treatment, minor complications, postoperative physiotherapy and subsequent contralateral CCLD) were intervening variables and were therefore not included in the statistical model.

2.5. Statistical analysis

Analyses were performed with a commercially available software progam (StataCorp, 2019). Continuous variables are presented as median (min-max) and categorical variables as number (percentage of total number of stifles by treatment method). A non-parametric Kruskal--Wallis one-way ANOVA was used to compare the difference in medians between the treatment groups, since graphical assessment of the continuous variables body weight and age showed deviance from normality. A Bonferroni correction was applied to adjust for pairwise comparison between the treatment groups with an alpha level of 0.0167 (0.05/3). Follow-up time was defined as time from surgery to first severe postoperative complication or to censoring. Dogs were censored if they were lost to follow-up, euthanized/dead for reasons unrelated to severe postoperative complications or had minor/no postoperative complications. The number and percentage of severe postoperative complications was calculated, and the difference in time to first severe postoperative complication in each treatment group described with Kaplan-Meier survival curves. Maximum follow-up time was set to 1000 days in the analysis.

A Cox proportional hazards model was applied to evaluate possible risk factors for severe postoperative complications. Collinearity between variables was tested by Goodman and Kruskal's gamma for categorical or dichotomous variables and by Spearman correlation coefficient for continuous variables. A hazard ratio (HR), 95 % confidence interval (CI) and p-value was calculated for each variable. All variables with $p < 0.2$ in univariable analyses were included in the initial multivariable model. Manual stepwise backward elimination was used for variable selection and a p-value of <0.05 was considered statistically significant. Biologically plausible interactions were considered for inclusion, and fixed effects for surgical technique (since main exposure variable) and hospital (to account for differences between the two VHs) were forced into the final model. As some dogs were included twice in the analysis due to bilateral treatment of CCLD, a frailty term for individual was explored. The Wald test was used to evaluate the significance of the predictors. Schoenfeld residuals for each variable in the final model were used to evaluate the assumption of proportional hazards, and a sensitivity analysis was performed to evaluate the assumption of individual censoring. The functional form of the predictors was evaluated by plotting of martingale residuals. In order to detect outliers and influential observations, deviance and scaled score residuals were plotted against time at risk, and the model was refitted without the suspected outlying observations. Linear combinations of the coefficients from the model were used to check for differences between the treatment methods after the final model was fitted.

3. Results

3.1. Animals and treatment

A total of 287 stifles (Hospital 1: 101, Hospital 2: 186) in 255 dogs met the inclusion criteria. The most common breeds were mixed-breed (n = 50), Rottweiler (n = 19), Labrador Retriever (n = 14), Golden Retriever (n = 13) and Poodle (n = 11). Of the 287 stifles, 141 were treated with LFS, 77 with TPLO and 69 with TTA (using cage and a plate (Montavon et al., 2002)). Four single session bilateral procedures (three LFS, one TPLO) were performed. Both age and body weight differed between treatment groups (7.5 years, 5.6 years and 3.9 years/11.7 kg, 42.2 kg and 29.0 kg for LFS, TPLO and TTA, respectively, $p < 0.001$ for both comparisons). For additional descriptive features of the included dogs and the surgical procedures, see Tables 1 and 2. The procedures were performed by 14 surgeons, of which two were board-certified and four residents (Table 3).

3.2. Complications

Severe postoperative complications occurred in 24/77 (31 %) stifles treated with TPLO, 31/141 (22 %) stifles treated with LFS and 17/69 (25 %) stifles treated with TTA. Surgical site infections or complications related to the surgical implants were the most common severe postoperative complications (Table 4). The first severe postoperative complication occurred within 215 days after surgery in 90 % of the stifles with such complications. In total, 8 stifles (2.9 %) suffered catastrophic complications during the follow-up period, of these 4 were treated with LFS, 3 with TPLO and 1 with TTA. Eight dogs had mild

Table 1
Descriptive features at time of cranial cruciate ligament disease diagnosis in 287 stifles (255 dogs), in a historical cohort study of severe postoperative complications after surgical treatment.

Variable	LFS (N = 141)		TPLO (N = 77)		TTA (N = 69)		Total	
Age (years)	7.53	(0.94–12.8)	5.63	(0.94–10.5)	3.89	(0.93–10.8)	6.1	(0.93–12.8)
Body weight (kg)	11.7	(3.3–49.3)	42.2	(19.0–80.3)	29.0	(9.8–66.0)	24.5	(3.3–80.3)
Overweight	47	(33.3)	25	(32.5)	12	(17.4)	84	(29.3)
Sex								
Female	*83*	*(58.9)*	*36*	*(46.8)*	*41*	*(59.4)*	*160*	*(55.8)*
Male	*58*	*(41.1)*	*41*	*(53.3)*	*28*	*(40.6)*	*127*	*(44.3)*
Insured	128	(90.8)	71	(92.2)	50	(72.5)	249	(86.8)
Lameness*								
<2 w	*41*	*(29.1)*	*11*	*(14.3)*	*18*	*(26.1)*	*70*	*(24.4)*
≥2 w	*100*	*(70.9)*	*66*	*(85.7)*	*51*	*(73.9)*	*217*	*(75.6)*
Comorbidities								
Orthopedic	34	(27.2)	30	(21.0)	18	(27.7)	82	(24.6)
Hip dysplasia	*9*	*(6.4)*	*2*	*(2.6)*	*5*	*(7.3)*	*16*	*(5.6)*
Patellar luxation	*22*	*(15.6)*	*0*	*(0.0)*	*3*	*(4.4)*	*25*	*(8.7)*
Osteochondrosis stifle	*0*	*(0.0)*	*6*	*(7.8)*	*1*	*(1.5)*	*7*	*(2.4)*
Other	*8*	*(5.7)*	*8*	*(10.4)*	*4*	*(5.8)*	*20*	*(7.0)*
Non-orthopedic	24	(15.2)	24	(16.8)	20	(30.8)	63	(18.9)

Continuous variables as median (min-max). Categorical variables presented as number of stifles (% total number of stifles by treatment method). LFS; lateral fabellotibial suture, TPLO; tibial plateau leveling osteotomy, TTA; tibial tuberosity advancement.
* before diagnosis.

Table 2
Details on the surgical treatment, severe postoperative complications and reoperations in a cohort of 287 stifles (255 dogs) with cranial cruciate ligament disease.

	LFS		TPLO		TTA		Total	
Number of surgeries	141	(49.1)	77	(26.8)	69	(24.0)	287	(100)
Surgeries at Hospital 1	*27*	*(19.2)*	*5*	*(6.5)*	*69*	*(100)*	*101*	*(35.2)*
Surgeries at Hospital 2	*114*	*(80.8)*	*72*	*(93.5)*	*0*	*(0.0)*	*186*	*(64.8)*
Joint inspection (%)	130	(92.2)	77	(100)	36	(52.2)	243	(84.7)
Arthrotomy	113	(80.1)	16	(20.8)	32	(46.4)	161	(56.1)
Arthroscopy	25	(17.7)	75	(97.4)	4	(5.8)	104	(36.2)
Meniscal injury	32	(22.7)	14	(18.2)	18	(26.1)	64	(22.3)
Antimicrobial use	97	(68.8)	75	(97.4)	69	(100)	241	(84.0)
Only peri-operative	*85*	*(87.6)*	*71*	*(94.7)*	*24*	*(34.8)*	*180*	*(74.7)*
Peri- and postoperative	*12*	*(12.4)*	*4*	*(5.3)*	*45*	*(65.2)*	*61*	*(25.3)*
Duration of anesthesia* (minutes)	145	(45–263)	280	(125–380)	198	(110–320)	185	(45–380)
Severe postoperative complication	31	(22.0)	24	(31.2)	17	(24.6)	72	(25.1)
Reoperation/joint lavage	22	(15.6)	15	(19.5)	11	(15.9)	48	(16.7)
Follow-up time (years)	2.1	(0–7.6)	1.9	(0–7.1)	3	(0–7.4)	2.3	(0–7.6)
Time to complication (days)	26	(4–768)	23	(2–444)	16	(1–525)	22	(1–768)

Time reported in median (range). Categorical variables as number of stifles (% total number of stifles by treatment method). LFS; lateral fabellotibial suture, TPLO; tibial plateau leveling osteotomy, TTA; tibial tuberosity advancement.
* n = 239.

Table 3
Number of procedures performed by each surgeon in a historical cohort study of 287 stifles (255 dogs) surgically created for cranial cruciate ligament disease.

	Hosital 1				Hospital 2			
Surgeon	LFS	TPLO	TTA	Total	LFS	TPLO	TTA	Total
B1	0	0	0	0	15	19	0	34
B2	0	0	0	0	23	16	0	39
E1	11	0	36	47	0	0	0	0
E2	0	0	0	0	6	10	0	16
E3	0	0	0	0	16	1	0	17
E4	0	0	0	0	22	8	0	30
E5	4	0	0	4	0	0	0	0
E6	0	0	0	0	19	7	0	26
E7	3	5	4	12	0	0	0	0
E8	3	0	21	24	0	0	0	0
R1	0	0	0	0	4	0	0	4
R2	1	0	0	1	1	1	0	2
R3	5	0	8	13	0	0	0	0
R4	0	0	0	0	8	10	0	18

B; board-certified; E; experienced surgeon, R; resident, LFS; lateral fabellotibial suture, TPLO; tibial plateau leveling osteotomy, TTA; tibial tuberosity advancement.

lameness that resolved with analgesic treatment and two dogs had a skin irritation close to the surgical wound that was treated with local antibiotics. These complications were classified as minor instead of severe.

3.3. Survival analysis

A Kaplan-Meier survival plot for the different treatment groups is presented in Fig. 1. Collinearity between variables was not detected. The results from the univariable Cox proportional hazards models are presented in Table 5. The final multivariable model included variables for treatment, hospital, age, and body weight (Table 6). Age and body weight were confounders for treatment method. There was a significant effect of surgical technique ($p = 0.0258$). The hazard of severe postoperative complications was significantly lower for dogs treated with TPLO compared with dogs treated with LFS ($HR = 0.37$, $p < 0.01$). No difference was found between TTA and LFS ($HR = 0.56$, $p = 0.361$) or between TPLO and TTA ($p = 0.495$, Wald test). In addition, the hazard increased with body weight ($HR = 1.05$, $p < 0.001$) and decreased with age ($HR = 0.91$, $p < 0.05$). The frailty term for individual did not reach statistical significance. The model validation did reveal some influential observations, but no violations of the model assumptions.

Table 4
Overview of severe postoperative complications in a historical cohort study of 287 stifles (255 dogs) surgically treated for cranial cruciate ligament disease.

Complication type	LFS (N = 141)		TPLO (N = 77)		TTA (N = 69)		Total (N = 287)	
Delayed wound healing	2	(1.4)	1	(1.3)	0	(0.0)	3	(1.0)
Implant-related	16	(11.3)	8	(10.4)	7	(10.1)	31	(10.8)
Meniscal injury	4	(2.8)	2	(2.6)	2	(2.9)	8	(2.8)
Osteomyelitis	0	(0.0)	0	(0.0)	2	(2.9)	2	(0.70)
Other	1	(0.7)	1	(1.3)	0	(0.0)	2	(0.70)
Patellar luxation	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.35)
Septic arthritis	4	(2.8)	3	(3.9)	0	(0.0)	7	(2.4)
Seroma	0	(0.0)	1	(1.3)	1	(1.4)	2	(0.70)
Surgical site infection	7	(5.0)	14	(18.2)	6	(8.7)	27	(9.4)
Tuberositas tibia fracture	0	(0.0)	0	(0.0)	2	(2.9)	2	(0.70)

Reported as number of stifles (% total number of stifles by treatment method). LFS; lateral fabellotibial suture, TPLO; tibial plateau leveling osteotomy, TTA; tibial tuberosity advancement. Each complication type is registered only once for each stifle, regardless of how many times it occurred. Other complications: the dog treated with TPLO had an acute postoperative lameness on the treated limb and was euthanized without further diagnostics, and the dog treated with LFS had suspected immune-mediated arthritis, even though septic arthritis could not be ruled out despite negative bacterial culture.

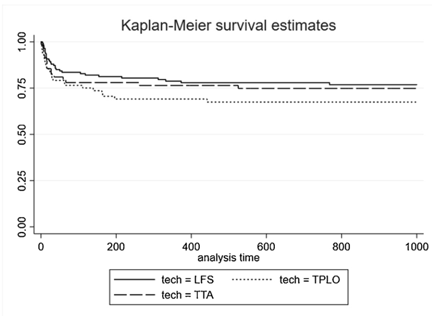

Fig. 1. Kaplan-Meier curves by treatment method describing time to severe postoperative complications (in days) after surgical treatment of CCLD in 287 stifles (255 dogs).

Table 5
Univariable Cox proportional hazards model for selection of variables in a historical cohort study assessing severe post-operative complications in 287 stifles (255 dogs) surgically treated for cranial cruciate ligament disease.

Variable	P-value
Age (years)*	0.01
Acute lameness*	0.02
Arthrotomy/arthroscopy	0.50
Body weight (kg)*	<0.01
Breed	0.84†
Hospital	0.22
Insurance*	0.50
Non-orthopaedic comorbidity*	0.94
Orthopaedic comorbidity*	0.10†
Overweight*	0.93
Sex	0.34
Surgeon experience	0.99†
Technique	0.29†
Year of treatment	0.42†

* at time of diagnosis.
† p-values from Wald test presented for multilevel categorical variables.

Table 6
Results from a multivariable Cox proportional hazards model assessing severe postoperative complications in a historical cohort study of 287 stifles (255 dogs) surgically created for cranial cruciate ligament disease.

Variable and level	Coefficient	HR	95 % CI	P
Treatment				0.026*
LFS		1	–	–
TPLO	−0.99	0.37	(0.18–0.76)	0.007
TTA	−0.57	0.56	(0.16–1.93)	0.361
Hospital				
Hospital 1		1	–	–
Hospital 2	0.5	1.65	(0.58–4.70)	0.345
Age (years)	−0.09	0.91	(0.83–1.00)	0.047
Body weight (kg)	0.05	1.05	(1.03–1.07)	<0.001

LFS; lateral fabellotibial suture, TPLO; tibial plateau leveling osteotomy, TTA; tibial tuberosity advancement.
Age and body weight at time of diagnosis.
* Wald-test.

4. Discussion

To the authors' knowledge, this cohort study is the first study comparing the occurrence of severe postoperative complications after TPLO, TTA and LFS. The overall frequency of severe postoperative complications was 25 %, but varied with surgical technique; for TTA it was 25 % which is higher than the 6.5–19.8 % reported in most other studies (Lafaver et al., 2007; Dymond et al., 2010; Hirshenson et al., 2012; Wolf et al., 2012; Costa et al., 2017; Hans et al., 2017), but below the 38.9 % reported by Christopher et al. (2013). The corresponding number for LFS was 22 %, but no comparisons could be made since previous studies evaluating complications after LFS lack classification of complication severity (Casale and McCarthy, 2009; Gordon-Evans et al., 2013). The frequency of severe postoperative complications after TPLO (31 %) was higher than the 3.1–27.8 % reported previously (Fitzpatrick and Solano, 2010; Christopher et al., 2013; Coletti et al., 2014; Garnett and Daye, 2014; Brown et al., 2016; Hans et al., 2017). Due to the different complication classification systems, caution is warranted at direct comparison of complications between studies. Even though the frequency of severe postoperative complications in the current study appears quite high, a wider definition of severe complications was used compared to several other studies, where a major complication was defined as a complication requiring surgical revision (Lafaver et al., 2007; Coletti et al., 2014; Garnett and Daye, 2014). However, the frequency of revision surgery in the current study (16.7 %) was also higher than the 3.1–12.3 % in other studies (Pacchiana et al., 2003; Lafaver et al., 2007; Casale and McCarthy, 2009; Coletti et al., 2014; Garnett and Daye, 2014). This may be due to different routines for when a revision surgery is recommended at different hospitals, but an inferior outcome with higher need for revision surgery in the current study cannot be excluded.

Tibial plateau leveling osteotomy had the highest frequency of severe postoperative complications. However, when adjusting for the confounding effects of age and body weight in the multivariable Cox proportional hazards model, TPLO was associated with a significantly decreased hazard of severe postoperative complications compared to LFS. This supports our hypothesis that both surgical technique, age and body weight are important risk factors for severe postoperative complications. The median body weight for dogs treated with TPLO was 42.2 kg, which is higher than in previous studies (Pacchiana et al., 2003; Fitzpatrick and Solano, 2010; Christopher et al., 2013; Coletti et al., 2014; Garnett and Daye, 2014; Brown et al., 2016). This could potentially explain the higher complication frequency in dogs treated by TPLO, since higher body weight has been reported as a risk factor for postoperative complications after CCLD surgery (Casale and McCarthy, 2009; Tuttle and Manley, 2009; Fitzpatrick and Solano, 2010; Steinberg et al., 2011; Taylor et al., 2011; Wolf et al., 2012; Coletti et al., 2014). A likely explanation is the higher mechanical stress on the implants in heavier dogs, and locking plates have been reported to reduce the risk for implant-related complications in heavy dogs (Solano et al., 2015; Chiu et al., 2019). In addition, activity restriction during the post-operative period could possibly be more difficult in large dogs, which could increase the risk of severe postoperative complications. It should be noted that, as smaller dogs were generally treated by LFS while larger dogs were treated by TPLO or TTA, the body weight of the dogs differed accordingly. Thus, the effect of each procedure on the hazard of severe postoperative complications is only applicable in the body weight range of each procedure. This should be acknowledged as a limitation to the generalizability of the results, and further studies of TPLO and TTA in small dogs are warranted.

In concordance with the results of a study by Casale and McCarthy (2009) evaluating complications after LFS, younger age was associated with an increased hazard of severe postoperative complications. Although injured tissue in general heals faster in young individuals compared to older (Wolf, 2010), younger dogs are also generally more active. Therefore, controlling the activity level during the postoperative period in young, active dogs is a well-known problem, and the results of our study implies this as an important challenge. Overall, these findings show that factors besides surgical technique should be considered when assessing risk of severe postoperative complications development in dogs after CCLD surgery.

The most common severe postoperative complications in the current study were implant-related, SSIs and subsequent meniscal injuries, which is in concordance with the most common severe complications reported for TTA, TPLO and LFS in other studies (Lafaver et al., 2007; Casale and McCarthy, 2009; Dymond et al., 2010; Fitzpatrick and Solano, 2010; Wolf et al., 2012; Christopher et al., 2013; Coletti et al., 2014; Hans et al., 2017). The frequency of SSI was 9.4 %, which is higher than the 3.9–8.4 % in previous reports (Casale and McCarthy, 2009; Fitzpatrick and Solano, 2010; Frey et al., 2010; Yap et al., 2015; Brown et al., 2016; Costa et al., 2017; Lopez et al., 2018). Administration of post-operative antibiotics has been identified as a protective factor for post-operative infection/inflammation and complications in some studies (Fitzpatrick and Solano, 2010; Frey et al., 2010; Hans et al., 2017), but not in others (Aiken et al., 2015; Yap et al., 2015). A lower occurrence of SSIs was seen after TTA (8.7 %) compared to TPLO (18.2 %) in the current study, which could be attributable to less administration of postoperative antibiotics in the TPLO group. However, due to the retrospective nature of the study, no causal conclusions could be drawn. A more stringent protocol for handling TPLO cases including modifications such as usage of triclosan-coated sutures, changes in distribution of intra- and postoperative antibiotics and mandatory usage of Elizabethan collars has been associated with a dramatic decrease in SSIs (Stine et al., 2018). Triclosan-coated sutures were not routinely used in the current study (data not shown).

The experience of the surgeon did not have a significant impact on the hazard of severe postoperative complications. The effect of surgeon experience is conflicting in the literature; some studies report no association between surgeon experience and complications (Pacchiana et al., 2003; Casale and McCarthy, 2009; Gordon-Evans et al., 2013), while others found higher risk of complications in surgeries performed by less experienced surgeons (Christopher et al., 2013; Lopez et al., 2018). The experience of the surgeon has also been associated with other factors, such as longer duration of surgery and anesthesia in less experienced surgeons (Freeman et al., 2017; Shaver et al., 2019), which are well known risk factors for SSI in dogs (Brown et al., 1997; Eugster et al., 2004). Information regarding duration of surgery was not available in the current study, and, as duration of anesthesia only was registered in 239 of the procedures (Table 2), it could not be included in the multivariable analysis without a substantial loss of observations and thus power. The duration of anesthesia was generally shorter for LFS procedures compared to TPLO and TTA, which could be due to the fact that the surgical procedures in TPLO and TTA are more time-consuming than LFS. In addition, postoperative radiographs were routinely taken before recovery from anesthesia in TPLO and TTA, but not LFS, which further increases anesthesia time.

Longer duration of anesthesia can also be expected if joint inspection is performed. In the current study all TPLO procedures included a joint inspection, most LFSs but only 52 % of the TTAs. Thus, evaluation of the menisci was not equally distributed between the procedures. Further, joint inspections were performed more often at VH1 than VH2. Bureau (2017) reported a low frequency of postoperative complications after TPLO without joint inspection, and an increasing number of surgeons have questioned the need for a routine meniscal examination (Jandi and Schulman, 2007; McCready and Ness, 2016). Others recommend joint inspection to confirm the diagnosis of CCLD and to evaluate meniscal injuries as well as other joint comorbidities (Ritzo et al., 2014). In the current study, joint inspection was included as a risk factor in the univariable analysis, but did not reach statistical significance.

Several additional study limitations should be mentioned. Due to the retrospective nature of the study, dogs were not randomly assigned to undergo a specific surgical technique. Thus, the treatment choice was influenced by inherent bias, including factors such as financial considerations, and perceived risk and prognosis associated with the treatment. It is likely that older dogs, and dogs with co-morbidities were managed with the cheaper and technically less challenging LFS method rather than the more expensive and complicated osteotomy techniques. Although measured factors which could have directed the treatment decision, such as insurance status, concurrent disease, body weight, and age of the dog were included in the analyses, unmeasured factors such as owners' financial considerations likely influenced our results. Even though dog owners and, in some cases, referring veterinarians were contacted for supplementary information, there is a risk that not all complications were identified, for example due to recall bias. It has been shown that dog owners report lower complication rates compared to those documented by veterinarians in medical records (except for catastrophic complications) (Christopher et al., 2013). In addition, financial considerations could have influenced the probability of owners bringing their dogs back for rechecks and complication treatment. However, as the outcome of this study was severe postoperative complications, we find it likely that most owners would have contacted the hospitals or recalled if their dog had been treated elsewhere. There is also a risk that complications such as postoperative meniscal damage remained undiagnosed, if no revision surgery was performed. Moreover, there is a risk that some of the implant-related complications were in fact deep SSIs, since samples for culture and sensitivity from the implants were not routinely taken in dogs with implant-related complications. The current study only evaluated severe postoperative complications, and therefore risk factors for minor postoperative or intra-operative complications were not assessed.

Postoperative antibiotics, as all other postoperative factors (such as physiotherapy), were intervening variables. Intervening variables occur after the main exposure but before the outcome in the causal sequence, and are regarded as an integrated part of the main exposure, which was the surgical intervention in the current study. Since the aim of this study was to assess the total effect of the surgical techniques on the hazard of postoperative complications, all intervening variables were excluded from the analysis. To assess the causality of postoperative antibiotic administration, a more strictly designed study aimed at this purpose with a prospective, randomized design would be necessary. A variable for hospital was forced into the final multivariable Cox proportional hazards model to account for unmeasured differences between the hospitals, such as differences in preoperative routines. We do, however, acknowledge that although adding a fixed effect for hospital ensures internal validity of the analysis, the retrospective nature of this study, together with the lack of standardized procedures for antimicrobial administration, could reduce the generalizability of the results to other hospitals.

It was not possible to evaluate the effect of duration of surgery or anesthesia or the pre- and perioperative antiseptic protocol on the hazard of postoperative complications, due to missing data. Since this was a retrospective study without predefined, standardized protocols, the level of details in the records varied. Although the information in the records was sufficient for a broader classification of the complications, a more detailed classification (i.e. type of implant-related complication) would introduce a high risk of misclassification bias. It is important to consider that retrospective studies are not suitable for assessing causality, but should rather be used to identify associations and generate hypothesis for future randomized, prospective studies.

The modification in the complication classification in the current study may limit the possibility of result comparison between studies. However, we believe that the modification is justified, since the reclassified complications had the characteristics of minor complications (i.e. skin irritation treated with local antibiotics or mild lameness that resolved with analgesic medication). These mild complications should have been classified as severe according to the classification scheme, but that would have biased the results towards a false high rate of severe postoperative complications. The surgical techniques for CCLD treatment at the hospitals during the study period included TPLO, TTA and LFS. In addition, a few dogs were treated with modified Maquet technique, but these dogs were excluded as there would have been low statistical power in any comparisons. Intra-articular stabilization procedures were not performed at the hospitals during the study period, and thus the included techniques could not be compared to intra-articular stabilization procedures or the modified Maquet technique.

In conclusion, osteotomy procedures had a lower hazard of severe postoperative complications compared to the extracapsular stabilization technique LFS, with the lowest hazard for TPLO. Moreover, age and body weight were identified as risk factors for severe postoperative complications and confounders for surgical technique. These findings highlight the importance of considering not only the surgical technique, but also other potential effect-modifying factors such as age and body weight of the dog when assessing risk for severe postoperative complications after CCLD surgery in observational orthopedic studies.

Author contributions

All authors contributed to the study design. KE and GSB registered the data under supervision from OH, AB and ERM. KE and GSB also carried out the data analysis and were major contributors to the manuscript, with substantial input from the other authors. All authors participated in the discussions and revisions of the entire text. All authors read and approved the final manuscript.

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Transparency document

The Transparency document associated with this article can be found in the online version.

Declaration of Competing Interest

None

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Disease-related and overall survival in dogs with cranial cruciate ligament disease, a historical cohort study

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ABSTRACT

Objective: To analyse the effect of treatment method and other risk factors on survival in dogs with cranial cruciate ligament disease (CCLD).
Methods: A historical cohort study of 333 dogs presenting with CCLD at two University Hospitals (2011–2016) was performed. Signalment, history, treatment and follow-up details were retrieved from medical records, dog owners and referring veterinarians. Treatment groups were defined; conservative or surgical with either lateral fabellotibial suture (LFS) or osteotomy procedures. Multivariable Cox proportional hazards models were applied to evaluate risk factors for disease-related and overall survival.
Results: Sixty-five dogs were conservatively managed, 125 treated with LFS and 143 with osteotomy techniques. At follow-up (autumn 2018), 164 dogs (49.3 %) were alive and 169 (50.7 %) were dead. Both final Cox proportional hazards models included variables for treatment, age, weight and hospital. In addition, the final disease-related model included a variable for orthopaedic comorbidity, while non-orthopaedic comorbidities and a time-varying effect for age on a linear scale were included in the overall survival model. Treatment method was found to have an effect on both disease-related and overall survival and surgical treatment was associated with a lower hazard than conservative treatment.
Conclusion: Survival in dogs with CCLD is influenced by treatment strategy, comorbidities, age and weight.

1. Introduction

Cranial cruciate ligament disease (CCLD) is one of the most common orthopaedic conditions in dogs (Johnson et al., 1994). Many factors including anatomical configuration, genetic and environmental factors are thought to affect the development of CCLD, but the exact aetiopathogenesis is still unclear (Whitehair et al., 1993; Duval et al., 1999; Witsberger et al., 2008; Taylor-Brown et al., 2015). The disease can be treated either conservatively or surgically, and osteoarthritis progresses in the affected joint regardless of treatment method (Schulz, 2012). More than 60 variations of surgical procedures have been described (Bergh et al., 2014), including lateral fabellotibial suture stabilisation (LFS), tibial plateau levelling osteotomy (TPLO) and tibial tuberosity advancement techniques such as the tibial tuberosity advancement (TTA) and the modified Maquet procedure (MMP). The most studied procedures are TPLO and LFS, followed by TTA, and there are only a few studies comparing long-term outcomes for more than two surgical techniques (Moore and Read, 1995; Conzemius et al., 2005; Christopher et al., 2013; Bergh et al., 2014; Mölsä et al., 2014). Although no general agreement on which surgical method yields the best outcome exists, there is some evidence in favour of TPLO according to a systematic review by Bergh et al. (2014). Only a limited number of studies have evaluated the outcome after conservative treatment (Pond and Campbell, 1972; Vasseur, 1984; Wucherer et al., 2013).

Most studies assessing the outcome after surgical treatment of CCLD have a follow-up time of less than six months and/or focus on risk

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factors for postoperative complications (Pacchiana et al., 2003; Stauffer et al., 2006; Fitzpatrick and Solano, 2010; Bergh et al., 2014; Hans et al., 2017). Information obtained from dog owner interviews/questionnaires and visual gait observation is commonly used for assessment of long-term outcome, while objective measurements such as force plate gait analysis and thigh circumference are less often reported (Bergh et al., 2014). In addition, several outcome evaluation tools aiming to incorporate different aspects of the clinical picture have been developed in recent years (Hyytiainen et al., 2018; Pinna et al., 2019). Common to all outcome measurement tools is that they aim to evaluate the degree of lameness, chronic pain or loss of function in the affected hind limb. This could potentially result in euthanasia in severe cases, if the degree of pain and loss of function is deemed unacceptable. However, there are currently no studies evaluating the effect of treatment strategy on life expectancy in dogs with CCLD, hence the risk of euthanasia in dogs with the disease is unknown.

The main objective of the current study was to estimate the effect of treatment method, other risk factors and potential confounders on survival in dogs with CCLD. We hypothesised that surgically treated dogs would have a favourable outcome compared to dogs treated conservatively.

2. Materials and methods

2.1. Study design

A historical cohort study was performed utilising electronic medical records of dogs with CCLD examined at two referral Veterinary University Hospitals (VHs) in Uppsala, Sweden and Oslo, Norway between January 1st, 2011 and December 31st, 2016.

2.2. Data collection

The medical records were reviewed between January 1st and August 31st, 2018. Routine clinical data, including history, age, breed, sex, body weight and treatment method, was retrieved. Neuter status and orthopaedic examination findings were registered in all records and hence not included. Although inconsistently recorded in the medical records, standardised written postoperative care and rehabilitation recommendations were available at both VHs and routinely provided to owners.

Follow-up information regarding additional complications, contralateral CCLD and date and reason for death/euthanasia was obtained from the medical records and by standardised telephone interviews with the owners between August 1st and October 15th, 2018. Furthermore, if additional information was needed, referring veterinarians were contacted (i.e. owner could not remember date or cause of euthanasia). Dates were recorded as 1st of the month if the exact date was unknown.

Inclusion criteria was a diagnosis of CCLD confirmed by either a positive cranial drawer test, a positive tibial thrust or by visual inspection of a ruptured cranial cruciate ligament by arthroscopy or arthrotomy. Exclusion criteria were: missing information about duration of lameness before treatment initiation, euthanasia at time of diagnosis, less than 14 days follow-up time, concurrent collateral ligament rupture, joint inspection revealing less than 10 % CCL rupture, diagnosis at the VHs but surgical treatment at another clinic, and surgical treatment of contralateral CCLD at the VHs prior to the study period.

2.3. Outcome

Reasons for death/euthanasia were retrospectively classified. Euthanasia related to CCLD was defined as all deaths where owners stated lameness from the affected hindlimb(s) as contributing to the decision of euthanasia. It was classified by the authors into five different subcategories; persistent lameness, subsequent contralateral CCLD, postoperative complications, guarded prognosis for return to full function, and other reasons. Classification of death/euthanasia unrelated to CCLD was performed according to Fleming et al. (2011), with a few modifications: the original categories for organ system and pathophysiological process were used, but additional categories for "high age" and "behaviour-related" were added. If the reason for death/euthanasia could not be classified, it was recorded as "unclassified" rather than excluded.

Factors related to the dog, the owner and the examining veterinarian can influence the decision of euthanasia, and hence, classification of cause of death can be uncertain. Consequently, analysis of overall survival was included to confirm the validity of the disease-related survival analysis.

2.4. Risk factors

Treatment method was defined as the main exposure variable. All dogs without surgical correction of CCLD were defined as conservatively treated. Surgically treated dogs were categorised into two treatment groups; LFS and osteotomy (TPLO, TTA and MMP).

A tentative causal diagram was made to identify possible confounding and intervening variables for the association of treatment method with the outcome. In addition, a change of > 20 % in the coefficients in the statistical model with the potential confounder present was used to assess confounding. All post-surgical related variables (such as postoperative complications and subsequent contralateral CCLD) were considered as intervening variables, and thus not considered for inclusion in the statistical analyses. The variables hospital, age, sex, weight, orthopaedic and non-orthopaedic comorbidities (present at the time of treatment initiation), lameness more than eight weeks prior to treatment initiation, insurance status, overweight (body condition score > 5/9, > 3/5 or subjectively judged as overweight by the examining veterinarian), laterality of the affected stifle, and joint exploration were considered as potential determinants for survival. The variable for orthopaedic comorbidity included separate categories for common causes of hindlimb lameness; patellar luxation, stifle osteochondrosis, hip dysplasia, in addition to other orthopaedic conditions.

2.5. Statistical analysis

All statistical analyses were conducted in Stata 15 (StataCorp, 2017). Graphical assessment of the continuous variables showed deviance from normality, hence continuous variables are presented as median (range). Categorical variables are presented as number (percentage). The one-sample test of proportions was used to compare the number of female and male dogs. Dogs with concurrent or subsequent contralateral CCLD were included as a single case at the time of first CCLD treatment at the VHs. Kaplan-Meier survival curves were used to describe differences in time-to-event for the treatment groups and the median time-to-event and censoring was calculated. Follow-up time was defined as the time from treatment initiation to death/euthanasia, or owner-contact/latest follow-up in the medical records when the dog was alive. Maximum follow-up time was set to 6 years (72 months) for the analyses.

Cox proportional hazards models were applied to estimate the effect of possible risk factors for disease-related and overall survival. Dogs alive at the end of the study period or lost to follow-up were censored. In addition, dogs that were dead/euthanised due to causes unrelated to CCLD were censored in the disease-related survival analysis. A single missing value was identified; a female Gordon setter without bodyweight recorded. In this case, the average bodyweight for female Gordon setters according to the breed standard[2] was used in the

[2] Fédération Cynologique Internationale breed standard Gordon setter,

Table 1
Descriptive features at time of diagnosis of 333 dogs with cranial cruciate ligament disease (2011-2016).

Variable	Surgery				Conservative		Total	
	LFS		Osteotomy					
Number of dogs (% of overall)	125	(37.5)	143	(43.0)	65	(19.5)	333	(100.0)
Dogs treated at Hospital 1	*25*	*(20.0)*	*77*	*(53.9)*	*19*	*(29.2)*	*121*	*(36.3)*
Dogs treated at Hospital 2	*100*	*(80.0)*	*66*	*(46.2)*	*46*	*(70.8)*	*212*	*(63.7)*
Age in years (min-max)	7.7	(0.9 – 12.8)	4.2	(0.9 – 10.7)	7.6	(0.2 – 13.3)	6.5	(0.2 – 13.3)
Weight in kg (min-max)†	11.3	(3.3 – 49.3)	35.0	(10.1 – 80.3)	17.9	(3.8 – 76.0)	23.6	(3.3 – 80.3)
Overweight (%)	41	(32.8)	35	(24.5)	19	(29.2)	95	(28.5)
Sex (%)								
Female	*74*	*(59.2)*	*71*	*(49.7)*	*40*	*(61.5)*	*185*	*(55.6)*
Male	*51*	*(40.8)*	*72*	*(51.3)*	*25*	*(38.5)*	*148*	*(44.4)*
Insured (%)	112	(89.6)	118	(82.5)	52	(80.0)	282	(84.3)
Stifle affected (%)								
Left	*60*	*(48.0)*	*82*	*(57.3)*	*28*	*(43.1)*	*170*	*(51.0)*
Right	*62*	*(49.6)*	*59*	*(41.3)*	*34*	*(52.3)*	*155*	*(46.6)*
Bilateral	*3*	*(2.4)*	*2*	*(1.4)*	*3*	*(4.6)*	*8*	*(2.4)*
Lameness > 8 w prior to treatment initiation (%)	47	(37.6)	74	(51.8)	33	(50.8)	154	(46.3)
Orthopaedic comorbidities (%)	34	(27.2)	30	(21.0)	18	(27.7)	82	(24.61)
Hip dysplasia	*7*	*(5.6)*	*9*	*(6.3)*	*2*	*(3.1)*	*18*	*(5.4)*
Patellar luxation	*19*	*(15.2)*	*2*	*(1.4)*	*5*	*(7.7)*	*26*	*(7.8)*
OC Stifle	*0*	*(0.0)*	*7*	*(4.9)*	*4*	*(6.2)*	*11*	*(3.3)*
Other	*8*	*(6.4)*	*12*	*(8.4)*	*7*	*(10.8)*	*27*	*(8.1)*
Non-orthopaedic comorbidities (%)	19	(15.2)	24	(16.8)	20	(30.8)	63	(18.9)

Categorical variables presented as number of dogs (% total number of dogs by treatment method if not specified). Continuous variables as median (min-max)..
LFS = Lateral Fabellotibial suture; OC = Osteochondrosis.
† Weight missing for one dog, N = 332.

analysis. Collinearity between variables was evaluated by Goodman and Kruskal's gamma for categorical or dichotomous variables and by Spearman rank-order correlation coefficient for continuous variables. A coefficient, hazard ratio (HR), its 95 % confidence interval and p-value, were calculated for each variable. All variables with $p < 0.15$ in univariable analyses were considered for inclusion in the multivariable models. A fixed effect for hospital was forced into the final models to account for differences between the two VHs.

A p-value of < 0.05 was considered statistically significant and manual stepwise backward elimination was applied for selection of variables. The Wald test was used to evaluate the significance of the predictors. Biologically plausible interactions were considered for inclusion. Schoenfeld residuals for each variable in the final models were used to evaluate the assumption of proportional hazards. If a violation of the proportional hazards assumption was identified and graphical assessment indicated a time-varying effect (TVE) of a variable, an interaction term between the variable and time on the appropriate scale was included in the model. Sensitivity analysis was performed to evaluate the assumption of individual censoring. Plots of martingale residuals were used to test the functional form of the predictors. Deviance and scaled score residuals were plotted against time at risk for detection of outliers and influential observations, respectively. The models were fit with and without the suspected outlying observations. Linear combinations of the coefficients from the models were used to check for differences between the treatment methods after the final models were fitted.

3. Results

3.1. Animals and treatment

Of the initial 436 dogs with CCLD identified within the study period, 333 (Hospital 1: 121, Hospital 2: 212) met the inclusion criteria and were enrolled in the study (see Table 1 for descriptive features). The most common breeds were mixed-breed (n = 66), Rottweiler (n = 24), Labrador Retriever (n = 15), Golden Retriever (n = 15) and Jack Russel Terrier (n = 13). There were more female than male dogs (p = 0.03). Of the 333 dogs, 65 (19.5 %) were conservatively treated, 125 (37.6 %) treated with LFS and 143 (42.9 %) treated with an osteotomy technique (71 TPLOs, 54 TTAs, 18 MMPs).

In total, 134/333 dogs (40.2 %) had a comorbidity recorded at the time of treatment initiation. The most common orthopaedic and non-orthopaedic comorbidities were patellar luxation and dermatological disease, respectively. Of the conservatively treated dogs, 18/65 (27.7 %) had concurrent orthopaedic conditions while 20/65 (30.8 %) had other non-orthopaedic diseases. The corresponding numbers for the LFS group were 34/125 (27.2 %) and 19/125 (15.2 %), and for the osteotomy group 30/143 (21.0 %) and 24/143 (16.8 %), respectively.

3.2. Outcome

At follow-up, 164/333 dogs (49.3 %) were still alive, while 169/333 (50.7 %) were dead or euthanised; 61/333 (18.3 %) of disease-related causes. Nineteen of the 65 (29.2 %) dogs in the conservatively treated group were dead due to disease-related causes, with corresponding numbers 19/125 (15.2 %) in the LFS group and 23/143 (16.1 %) in the osteotomy group (Table 2). Concurrent comorbidities contributed to the decision in 9/19 (47.4 %) conservatively treated dogs, 6/19 (31.6 %) dogs treated by LFS and 7/23 (30.4 %) dogs treated with osteotomy. None of the dogs excluded due to < 14 days follow-up time were recorded as dead/euthanised. The most common disease-related reason for euthanasia was persistent lameness (see Table 3 for further details). The most common non-disease-related reasons were high age or related to the urogenital organs, gastrointestinal system or the musculoskeletal system (lameness of the affected hindlimb excluded).

3.3. Survival analysis

Kaplan-Meier survival curves for disease-related and overall survival in the different treatment groups are presented in Fig. 1. Collinearity between variables was not detected.

The final multivariable disease-related survival model included

(*footnote continued*)
accessed 13.02.2019: http://www.fci.be/Nomenclature/Standards/006g07-en.pdf

Table 2
Treatment and follow-up details of 333 dogs with cranial cruciate ligament disease (2011-2016).

Variable	Surgery				Conservative		Total	
	LFS (N = 125)		Osteotomy (N = 143)		(N = 65)		(N = 333)	
Follow-up time in months (min-max)	34.0	(0.8 – 91.3)	36	(0.5 – 89.3)	23.5	(0.6 – 90.4)	34	(0.5 – 91.3)
Bilateral rupture (% of dogs with unilateral CCLD)*	47	(38.5)	49	(34.8)	10	(16.1)	106	(32.6)
Joint inspection (%)	115	(92.0)	104	(72.7)	5	(7.7)	224	(67.3)
Hospital 1	*16*	*(64.0)*	*38*	*(49.4)*	*4*	*(21.1)*	*58*	*(47.9)*
Hospital 2	*99*	*(99.0)*	*66*	*(100.0)*	*1*	*(2.2)*	*166*	*(78.3)*
Arthrotomy (%)	101	(80.1)	42	(29.4)	2	(3.1)	145	(43.5)
Arthroscopy (%)	21	(16.8)	73	(51.1)	3	(4.6)	97	(29.1)
Meniscal injuries (%)	29	(23.2)	29	(20.3)	1	(1.5)	59	(17.7)
Post-operative complications (%)	32	(25.6)	52	(36.4)	NA		NA	
Dogs alive (%)	69	(55.2)	76	(53.2)	19	(29.3)	164	(49.3)
Dogs dead/euthanised (%)	56	(44.8)	67	(46.8)	46	(70.7)	169	(50.7)
CCLD-related	*19*	*(15.2)*	*23*	*(16.1)*	*19*	*(29.2)*	*61*	*(18.3)*
Other causes	*37*	*(29.6)*	*44*	*(30.7)*	*27*	*(41.5)*	*108*	*(32.4)*
Months to CCLD-related euthanasia (min-max)	19.9	(2.3 – 45.1)	21.9	(0.5 – 68.1)	2.4	(0.6 – 74.0)	15.6	(0.5 – 74.0)
Months to censoring (min-max)	37.4	(0.8 – 91.3)	38.7	(0.8 – 89.2)	25.4	(0.6 – 90.3)	36.2	(0.6 – 91.3)

Continuous variables reported as median (range), categorical variables as number of dogs (percentage).
CCLD = Cranial Cruciate Ligament Disease; LFS = Lateral Fabellotibial suture; NA = Not applicable; OC = Osteochondrosis.

Table 3
Classification of cause of cranial cruciate ligament disease-related euthanasia in 61 dogs from a cohort study of 333 dogs (2011-2016).

Reason for euthanasia	CCLD only	Comorbidity	Combined
	N (%)	N (%)	N (%)
Persistent lameness	13 (52.0)	12 (48.0)	25 (41.0)
Contralateral CCLD	16 (94.1)	1 (5.9)	17 (28.9)
Other	2 (22.2)	7 (77.8)	9 (14.8)
Post-operative complications	7 (87.5)	1 (12.5)	8 (13.1)
Guarded prognosis	2 (100.0)	0 (0.0)	2 (3.3)
Total	40 (65.6)	21 (34.4)	61 (100)

CCLD = Cranial cruciate ligament disease.
Comorbidity = additional non – CCLD related factors contributing to the decision of euthanasia.
Guarded prognosis = prognosis perceived as guarded for return to full function by either examining veterinarian or owner.

variables for treatment method, orthopaedic comorbidities, age, weight and hospital (Table 4). The hazard for dogs treated by osteotomy was lower than for the conservatively treated dogs (HR 0.40, p = 0.012). It was also lower for the dogs treated by LFS (HR 0.56, p = 0.109). No statistical difference was found between LFS and osteotomies (p = 0.370). The hazard increased with other orthopaedic comorbidities (HR 3.09, p = 0.001), increasing age (HR 1.12, p = 0.039) and increasing body weight (HR 1.03, p = 0.001). The model validation for the disease-related survival model did not reveal violations of the model assumptions.

In the final multivariable overall survival model, the assumption of proportional hazards was violated for age. The graphical assessment indicated that the effect of age increased on a linear time scale. Thus, a TVE interaction between age and time was included in the overall survival model. The variables for treatment method, non-orthopaedic

Table 4
Results from a multivariable Cox proportional hazards model of disease-related survival in a cohort of 333 dogs with cranial cruciate ligament disease.

Variable and level	Coeff.	HR	95 % CI	P
Treatment				0.035†
Conservative		*1.00*	–	–
LFS	*−0.58*	*0.56*	*(0.28 – 1.14)*	*0.109*
Osteotomy	*−0.91*	*0.40*	*(0.19 – 0.81)*	*0.012*
Hospital				
Hospital 1		*1.00*	–	–
Hospital 2	*0.20*	*1.21*	*(0.65 – 2.25)*	*0.547*
Orthopaedic comorbidity				< 0.001†
None		*1.00*	–	–
Patellar luxation	*0.45*	*1.57*	*(0.52 – 4.73)*	*0.420*
Hip dysplasia	*0.09*	*1.10*	*(0.34 – 3.59)*	*0.873*
OC Stifle	*−0.24*	*0.78*	*(0.22 – 2.80)*	*0.706*
Other	*1.12*	*3.09*	*(1.59 – 6.00)*	*0.001*
Age (years)	0.11	1.12	(1.01 – 1.25)	0.040
Weight (kg)	0.03	1.03	(1.01 – 1.05)	0.001

During the follow-up period a total of 61/333 dogs suffered disease-related euthanasia. Age, weight and orthopaedic comorbidities at time of diagnosis.
HR = Hazard ratio, LFS = Lateral fabellotibial suture technique, OC = Osteochondrosis.
† Wald-test.

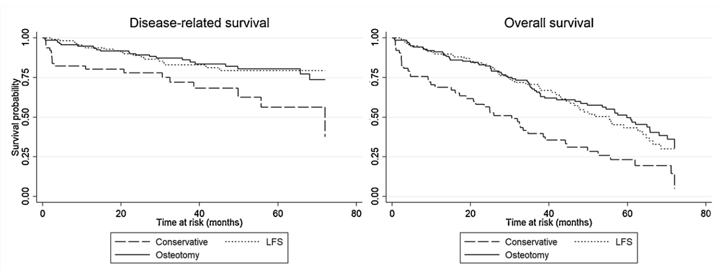

Fig. 1. Kaplan-Meier curves by treatment method describing survival in a cohort of 333 dogs with cranial cruciate ligament disease.

Table 5
Results from a multivariable Cox proportional hazards model of overall survival in a cohort of 333 dogs with cranial cruciate ligament disease.

Variable and level	Coeff.	HR	95 % CI	P
Treatment				0.002†
Conservative		*1.00*	–	–
LFS	*−0.63*	*0.53*	*(0.35−0.80)*	*0.003*
Osteotomy	*−0.63*	*0.53*	*(0.35−0.81)*	*0.003*
Hospital				
Hospital 1		*1.00*	–	–
Hospital 2	*0.20*	*1.22*	*(0.85−1.77)*	*0.278*
Non-orthopaedic comorbidity	0.42	1.53	(1.05−2.22)	0.028
Age (years)	0.11	1.12	(1.01−1.24)	0.028
Weight (kg)	0.03	1.03	(1.02−1.04)	< 0.001
TVC (age)	0.00	1.00	(1.00−1.01)	0.006

During the follow-up period a total of 169/333 dogs where dead/euthanised. Age, weight and non-orthopaedic comorbidities recorded at time of diagnosis. HR = Hazard ratio, LFS = Lateral fabellotibial suture technique, TVC = Time-varying covariate.
† Wald-test.

comorbidities, age and weight had a significant effect on survival. The final multivariable overall survival model is presented in Table 5.

None of the tested interactions were significant in either model. In both the disease-related and overall survival model, weight and age were confounded with treatment method.

4. Discussion

Chronic clinical dysfunction due to persistent lameness resulting in euthanasia is the most serious outcome of CCLD. This study is the first to evaluate survival in dogs with CCLD. In total, 18.3 % of the dogs were dead/euthanised of disease-related causes within the follow-up time, which is substantially higher than the 2% reported by Mölsä et al. (2013). Due to differences in study design and study samples, a direct comparison of results is inappropriate and should be avoided. For example, the study by Mölsä et al. (2013) was based on a questionnaire completed by owners of 253 surgically treated dogs (followed for a mean of 2.7 years), and it could be that owners of euthanised dogs were less likely to return such a questionnaire. At one-year follow-up, 43/333 (12.9 %) dogs in the current study had died or been euthanised. This finding supports the fact that exclusion of euthanised dogs has the potential to bias the results in long-term studies evaluating clinical function of dogs with CCLD.

Results from both the disease-related and the overall survival model showed a favourable outcome for surgically treated dogs, with the lowest hazard for dogs treated with osteotomy procedures. These findings seem to be in line with the current evidence regarding long-term outcome of dogs with surgically treated CCLD. The systematic review by Bergh et al. (2014) concluded that, although the evidence is too sparse to compare the effect of different treatment interventions, there is some evidence in favour of TPLO as the preferred surgical technique. One of the few randomised blinded controlled clinical trials included in the systematic review was a study by Gordon-Evans et al. (2013), which reported 1-year outcome after LFS and TPLO surgery in 80 dogs. The results indicated that both groups improved after surgery and 93 % of owners were very satisfied after TPLO and 75 % after LFS. Moreover, the superiority of osteotomy techniques in regard to functional outcomes is also supported by the views of veterinary practitioners and surgeons; a 2016 survey of American veterinary orthopaedic surgeons found that TPLO was the preferred surgical technique for dogs > 15 kg (von Pfeil et al., 2018).

Further, in the current study there was a risk of treatment failure resulting in euthanasia following conservative treatment. This finding is supported by a study by Wucherer et al. (2013) including overweight dogs > 20 kg followed for one year, where conservative treatment resulted in a less favourable outcome than TPLO. It should, however, be noted that the outcome was reported as successful in two-thirds of the conservatively treated dogs. Since body weight was identified as a risk factor in both survival models in the current study, with a lower hazard for smaller dogs, it seems reasonable that conservative management could still be a viable alternative in smaller dogs. These arguments can explain why conservative treatment is commonly chosen for small dogs, as reported in a recent UK surgeon survey by Comerford et al. (2013). However, bodyweight is a widely known risk factor for survival in dogs (irrespective of CCLD); large and giant breed dogs generally have a shorter life span than smaller dogs (O'Neill et al., 2013). In the context of CCLD, the lower hazard for smaller dogs observed in the current study could potentially be confounded by the generally longer life expectancy in smaller dogs.

Orthopaedic comorbidity increased the risk of failure in the disease-related survival model. A possible explanation is that the outcome might be influenced by the co-existing condition. In addition, owners of dogs with concurrent orthopaedic conditions could have perceived the prognosis as more guarded than owners of dogs with an isolated CCLD. Thus, they could be less motivated to pursue further treatment. In the overall survival model, non-orthopaedic comorbidity increased the risk of failure. This would be expected, since other diseases such as idiopathic epilepsy and heart failures are common reasons for euthanasia/death in dogs, thereby influencing the overall survival (Bonnett et al., 2005). As with the orthopaedic comorbidities, owners of dogs with non-orthopaedic diseases might be more reluctant to proceed with treatment of CCLD. A similar reasoning is likely to explain why the hazard of death/euthanasia increased with age in both survival models. For the overall survival, the effect of age on the hazard of death/euthanasia increased over time, implying that death/the decision of euthanasia was more influenced by age in older dogs compared with younger.

In our study, surgeons with different levels of experience performed the procedures. The literature provides conflicting results regarding the impact of the surgeon's experience on the outcome. While a few studies have reported a positive correlation between surgeon experience and outcome (Christopher et al., 2013), no association has been found in several others (Pacchiana et al., 2003; Conzemius et al., 2005; Casale and McCarthy, 2009; Gordon-Evans et al., 2013; Wilson et al., 2018). It was not possible to determine the level of experience of the surgeons in the present study; thus, the effect on survival could not be evaluated and this should be acknowledged as a limitation. However, including surgeons with different levels of experience could increase the external validity of this study, since the outcome after procedures performed by surgeons with variable levels of experience may more accurately reflect common practice.

Joint exploration with meniscal inspection is generally recommended and has been performed in most studies of surgically treated CCLD in dogs (Conzemius et al., 2005; Stauffer et al., 2006; Fitzpatrick and Solano, 2010). It should be noted that joint exploration was rarely performed in the conservatively treated dogs in the current study. As such, undetected meniscal injury is a potential confounding bias in the conservatively treated group.

There are some additional limitations in the current study that should be mentioned. Importantly, survival only represents one aspect of treatment outcome. The quality of life (QoL) for dogs with CCLD should also be taken into consideration. Several standardised clinical metrology instruments measuring chronic pain (HCPI and CBPI) or function (COI) have been evaluated for assessment of musculoskeletal disorders in dogs (e.g. Brown et al. (2007); Brown (2014); Hielm-Bjorkman et al. (2009)). However, due to the long follow-up time in our study, a high percentage of the dogs were dead at the time of follow-up. Consequently, such assessments would only have provided results for a selected group of dogs.

Moreover, the categorisation of the reasons for death/euthanasia relied on the authors' judgement, without further investigation or post-mortem examinations. A decision of euthanasia is often complex and disease-related survival is not a completely objective endpoint. However, the results concerning disease-related survival were supported by the overall survival model. Any misclassification bias is consequently likely to be non-differential and only reduce the likelihood to observe associations between exposures and the outcome.

The animal welfare legislation in Norway and Sweden supersedes the EU regulations with more stringent requirements and a generally higher standard for animal welfare than many other European countries (Veissier et al., 2008). Thus, in both countries, it is common to regard lameness as a welfare concern, and euthanasia is likely to be recommended when limb function is considered unacceptable. We believe this is important for the generalizability of the results in the current study.

As this study was not conducted on a randomised group of patients, the decision on which treatment to take for CCLD was not random. Thus, both the initial treatment choice and the final decision of euthanasia was likely influenced by inherent bias, including financial considerations, and perceived risk and prognosis associated with the treatment. It is likely that older dogs, and dogs with co-morbidities were managed with cheaper methods (conservative, LFS) rather than the more expensive osteotomy techniques. Likewise, owners investing less in their pet may be more likely to choose euthanasia, rather than treatment, for co-morbidities which are treatable, but comprehensive and/or expensive to treat at the end of life. Since the present study was conducted at referral hospitals, a selection bias towards complicated cases cannot be excluded. Thus, it is possible that the success of conservative treatment in the target population may be better than in the current study. As shown in Table 1, relatively more osteotomy procedures were performed at hospital 1 compared to hospital 2. Thus, choice of surgical technique was to some degree dependent on where the procedure was performed, which is most likely due to differences in routines and technique familiarity at the hospitals, in addition to the preference of individual surgeons. This is in line with the survey by von Pfeil et al. (2018) and illustrates that not only the signalment of the dog, but also the surgeon's preference are important determinants for treatment choice. Although factors which could have directed the treatment decision, such as hospital, insurance status, concurrent disease, weight and age of the dog were included in the analysis, unmeasured factors such as owners' financial considerations and perceived prognosis of both owners and clinicians likely influenced our results.

5. Conclusion

Disease-related euthanasia due to CCLD was not uncommon in this population of dogs, which shows that CCLD can affect life expectancy. Both treatment strategy and variables related to signalment and history of the dog were identified as risk factors for death/euthanasia. Surgically treated dogs had a lower hazard compared to conservatively treated dogs, which is in concordance with our hypothesis. In addition, comorbidity and increasing age and weight increased the hazard. Information regarding life expectancy in relation to risk factors is valuable facing a decision about treatment of CCLD.

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Author contributions

All authors contributed to the study design. KE and GSB registered the data under supervision from OH, AB and ERM. KE and GSB also carried out the data analysis and interpretation under supervision from RK with contribution from UE, ES and JH. KE and GSB was major contributors to the manuscript, with substantial input from the other authors. All authors participated in the discussions and revisions of the entire text. All authors read and approved the final manuscript.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.prevetmed.2020.105057.

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Supplementary table 1. Cranial cruciate ligament surgeries performed at two Veterinary University Hospitals in a cohort of 333 dogs with surgically and conservatively treated CCLD.

	LFS				TPLO				TTA				MMP			
Year	Surg	Pro	Median	(min-max)	Surg	Pro	Median	(min-max)	Surg	Pro	Median	(min-max)	Surg	Pro	Median	(min-max)
2011	8	24	5	(1-6)	6	15	5	(1-5)	3	12	8	(1-8)	1	5	5	(5-5)
2012	8	19	3	(1-4)	4	13	4	(2-4)	2	15	10	(5-10)	2	2	1	(1-1)
2013	8	25	5	(1-6)	5	10	3	(1-3)	2	10	6	(4-6)	1	2	2	(2-2)
2014	6	14	4	(1-4)	5	9	2	(1-3)	3	9	5	(2-5)	1	3	3	(3-3)
2015	8	16	2.5	(1-5)	3	8	3.5	(1-4)	2	6	4	(2-4)	2	5	4	(1-4)
2016	8	27	7	(1-8)	4	16	6	(1-8)	1	2	2	(2-2)	1	1	1	(1-1)
Total	**15**	**125**	**4**	**(1-8)**	**10**	**71**	**3**	**(1-8)**	**4**	**54**	**5**	**(1-10)**	**2**	**18**	**3.5**	**(1-5)**

Surg = Number of individual surgeons, Pro = Total number of procedures, Median (min-max) = Median number of procedures/surgeon
CCLD = Cranial cruciate ligament disease, LFS = Lateral fabellotibial suture, TPLO = Tibial plateau leveling osteotomy, TTA = Tibial tuberosity advancement, MMP = Modified maquet procedure

Supplementary table 2. Univariable Cox proportional hazard analysis for selection of variables to be included in a multivariable Cox proportional hazards model of disease-related survival in a cohort of 333 dogs with cranial cruciate ligament disease

Variable	P-value
Age (years)	0.019
Lameness >8 w prior to treatment	0.008
Hospital	0.074
Joint inspection	0.124
Insurance	0.144
Laterality of affected limb[†]	0.774
Meniscal injury	0.250
Non-orthopaedic comorbidiy	0.963
Orthopaedic comorbidity[†]	0.014
Overweight	0.900
Sex	0.135
Treatment[†]	0.003
Year of treatment[†]	0.464
Weight (kg)	0.034

[†]p-value from Wald test presented for multilevel categorical variables

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The aims of this thesis were to investigate the epidemiology of stifle joint disease (SJD) in dogs and to evaluate outcomes after treatment for cruciate ligament disease (CLD). The results showed that the risk of SJD and CLD varied with breed, and that breeds of molosser type were overrepresented among those at high risk of CLD. The risk of postoperative complications and euthanasia in dogs with CLD was affected by treatment method, and patient-related factors such as age and bodyweight.

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