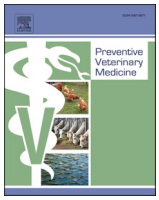
Preventive Veterinary Medicine 242 (2025) 106589

Contents lists available at ScienceDirect

Preventive Veterinary Medicine

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



The epidemiology of mast cell tumours in insured dogs in Sweden

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ARTICLE INFO

Keywords:
Canine
Dog
Mast cell tumour
Mastocytoma
Cancer
Tumour
Insurance
Breed risks
Cohort

ABSTRACT

Background: Mast cell tumour (MCT) is the most common skin neoplasia in dogs. This study aimed to explore the incidence rate, cause-specific mortality rate and risk factors (breed, age, gender) for MCT in insured dogs in Sweden (2011–2016).

Results: The study population of this cohort study included just over 600,000 dogs, which either were insured for veterinary care, life, or both. There were 917 dogs with veterinary care claims for MCT, and the incidence rate was 5.23 (95 % confidence interval (CI): 4.90–5.58) cases per 10,000 dog-years at risk (DYAR). The risk of MCT was higher in females than in males (relative risk (RR) 1.29, 95 % CI: 1.13–1.48, $P < 0.001$). The breeds at highest risk were the Dogo Argentino (RR 30.0, 95 % CI 9.70–70.2) and Boxer (RR 9.78, 95 % CI 7.02–13.3), while the Jämthund (RR 0.10, 95 % CI 0.01–0.35) and Cavalier King Charles spaniel (RR 0.06, 95 % CI 0.00–0.35) had the lowest risk. The median age at first diagnosis was 7.93 (range 0.44–15.4) years. In total, 11.6 % of the affected dogs suffered multiple MCT events. The cause-specific mortality rate was 0.79 (95 % CI: 0.63–0.97) deaths per 10,000 DYAR, and 87 of all dogs that were covered by life insurance died of MCT-related causes at a median age of 8.33 years (range 2.16–11.7). The Shar-pei (RR 51.5, 95 % CI: 13.7–137.0) had the highest risk of MCT-related death.

Conclusions: MCT mainly affected middle-aged to older dogs, and large breed-related differences in the risk of MCT and MCT-related death were found.

1. Background

Mast cell tumour (MCT) is one of the most common skin neoplasms in dogs, accounting for 11.0–21.3 % of all skin tumours and 6.5–7 % of all tumours in total (Bostock, 1986; Rothwell et al., 1987; Er and Sutton, 1989; Kaldrymidou et al., 2002; Mukaratirwa et al., 2005; Bronden et al., 2010b; Villamil et al., 2011; Gruntzig et al., 2016; Smiech et al., 2017, 2018; Graf et al., 2018; Martins et al., 2022). The majority of MCTs in dogs occur in the dermis or the subcutaneous tissue (Welle et al., 2008; Gruntzig et al., 2016). Tumour appearance varies; some are well-circumscribed, firm, raised, and slow growing, while some are erythematous, ulcerated, and grow rapidly (London and Seguin, 2003; Welle et al., 2008; Willmann et al., 2021). The degree of malignancy is evaluated histopathologically using the Patnaik and Kiupel systems (Patnaik et al., 1984; Kiupel et al., 2011). High-grade tumours are associated with shorter time to metastasis, additional MCT development (recurrence at the original surgical site or MCT occurring elsewhere), and survival time (Kiupel et al., 2011).

The aetiology of MCT is likely multifactorial and not yet fully understood (Welle et al., 2008). The genetic background and risk factors for MCT development have been explored in previous research (Shoop et al., 2015; Biasoli et al., 2019; Vozdova et al., 2020; Rodriguez et al., 2023; Zmorzynski et al., 2024). Several breeds are predisposed, including the Boxer, Pug, Staffordshire bull terrier, Boston terrier, Golden retriever, Shar-pei, and French bulldog, which supports a genetic component in the disease aetiology (Welle et al., 2008; Shoop et al., 2015; Rodriguez et al., 2023). Mast cell tumours generally affect middle-aged to older dogs, with a reported median age at diagnosis of 7–9 years (Patnaik et al., 1984; Baker-Gabb et al., 2003; Welle et al., 2008; Kiupel et al., 2011; Shoop et al., 2015). Most studies report no sex predisposition (Baker-Gabb et al., 2003; Welle et al., 2008; Shoop et al., 2015; Gruntzig et al., 2016), though one study observed higher odds of

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https://doi.org/10.1016/j.prevetmed.2025.106589
Received 5 December 2024; Received in revised form 30 May 2025; Accepted 30 May 2025
Available online 31 May 2025

high-grade tumours in males (Mochizuki et al., 2017). Approximately 40 % of dogs with MCT are affected by paraneoplastic signs from the gastrointestinal tract such as anorexia, diarrhoea, vomiting, haematochezia, melena, and abdominal pain due to the release of vasoactive substances from the cytoplasmic granules of the mast cells (Welle et al., 2008; Ledur et al., 2023). In addition, over 50 % are reported to have clinical signs associated with local mast cell degranulation, such as pruritus (Ledur et al., 2023).

Several studies have explored the epidemiology of MCT in dogs by using different data sources, such as data from primary-care veterinary practices (Shoop et al., 2015), a referral veterinary practice (White et al., 2011), a veterinary teaching hospital (Pierini et al., 2019), pet tumour registries (Bronden et al., 2010a; Rodriguez et al., 2023), and histopathological data from laboratories (Mochizuki et al., 2017; Martins et al., 2021; Aupperle-Lellbach et al., 2022). All data sources have inherent limitations, such as referral bias, limited representation of the general dog population, and a poorly defined denominator population for data from referral veterinary practices and cancer registries (O'Neill et al., 2014). Insurance data can be used for epidemiological studies of disease morbidity and mortality in dogs. A benefit of using insurance data is the inclusion of both the healthy background population and clinical events (Egenvall et al., 2009), although the representation of the general dog population might be poor in case of low insurance coverage (Egenvall et al., 2009; O'Neill et al., 2014). Sweden has the highest insurance coverage of the dog population worldwide: approximately 90 % of the dog population was insured in 2017 (Agria Djurförsäkring, 2017). Agria Djurförsäkring is a leading pet insurance company based in Sweden with operations in nine markets across Europe, and insured approximately 38 % of the Swedish dog population in 2016 (Olsson, 2020). Data from Agria Djurförsäkring have been used in epidemiological studies of conditions such as dystocia, atopy, kidney disease, upper respiratory tract disorders, cruciate ligament rupture, and adrenocortical insufficiency (Bergström et al., 2006; Nødtvedt et al., 2006; Pelander et al., 2015; Hanson et al., 2016; Engdahl et al., 2021; Dimopoulou et al., 2023).

This study aimed at exploring the incidence and cause-specific mortality rate of MCT and risk factors for MCT development in a population of dogs insured by Agria Djurförsäkring in Sweden, 2011–2016. Additional aims were to describe the occurrence of other diagnoses in dogs with MCT, with a focus on gastrointestinal and skin disorders, and explore the occurrence of multiple MCT events (defined as two MCT diagnoses at least three months apart).

2. Methods

2.1. Data

This cohort study included dogs insured by Agria Djurförsäkring in Sweden between 1 January 2011 and 31 December 2016. Dogs could be insured for veterinary care, life, or both. The veterinary care insurance reimbursed costs associated with veterinary care (such as examinations, treatments, and diagnostics), and the life insurance provided compensation equivalent to the dog's value in case of death or euthanasia. The data included information about the type of insurance policy, age, breed, sex (female/male, information about neuter status was unavailable), date of insurance enrolment and termination, and dates and diagnostic codes for veterinary care claims and life insurance settlement during the study period (if any). The breeds and breed groups were categorised according to the Fédération Cynologique Internationale and the Swedish Kennel Club (Federation Cynologique Internationale, 2024; Svenska Kennelklubben, 2024a). Dogs were excluded in case of missing information regarding age, breed, date of insurance enrolment, or sex.

The date of and age at first MCT diagnosis were based on the date of the first registered claim for MCT during the study period. If a dog had more than one claim for MCT, it was considered having multiple MCT events if the claims were at least three months apart (either a recurrence, a prolonged treatment of the initial tumour, or a new MCT). The three-month limit was chosen based on results from Baker-Gabb et al. (2003), reporting a median time to recurrence of three months in dogs surgically treated for MCT.

The veterinary costs over rolling 125-day periods had to exceed the insurance deductible for an insurance claim to be reimbursed. If receipts from several veterinary appointments were submitted together, these were usually recorded as separate claims on the same date. Each insurance claim had one or several diagnostic codes attached, chosen by the examining veterinarian from a national hierarchical diagnostic registry (Svenska Djursjukhusföreningen, 1993; Egenvall et al., 2009). Two diagnostic codes were available for MCT: 1. Mast cell tumours of the skin and subcutaneous tissues and 2. Mastocytoma.

Depending on breed, the life insurance policy terminated at eight, ten, or twelve years of age (Supplementary Table 1). Enrolment in veterinary care insurance had no age limit, while the dogs had to be enrolled in life insurance before four (for breeds with insurance termination at eight years of age) or six years of age (for all other dog breeds). Life insurance settlement required a certificate from a veterinarian. It was not possible to discriminate between natural death and euthanasia.

2.2. Statistical analysis

The data analysis was performed in R version 4.2.1 (R Core Team, 2022). Continuous variables are reported as median (IQR, range), and categorical variables as numbers and percentages per category. The Shapiro-Wilk test and visual assessment of histograms were used to assess the normality of continuous variables. Age differences were explored with the Wilcoxon rank sum test. The total dog-years at risk (DYAR) for the insured dog population were calculated by summing the insurance duration for all dogs during the study period. The incidence rate of and risk factors for MCT were evaluated using veterinary care claims in veterinary care insured dogs, while the cause-specific mortality of and risk factors for MCT-related death were evaluated using life claims in life-insured dogs. In addition, the time from first MCT diagnosis to death was evaluated in dogs with both veterinary care and life insurance.

The first MCT claim during the study period in dogs with veterinary care insurance was used for incidence calculation, and the DYAR in dogs with MCT were based on the time to that claim. Time at risk for veterinary care insured dogs without claims for MCT equals their total time of insurance during the study period. The incidence rate was expressed as the number of dogs with MCT per 10,000 DYAR. In dogs with life insurance, time to MCT-related death was used for the calculation of cause-specific mortality, which was expressed as the number of dogs that died of MCT-related causes per 10,000 DYAR.

The relative risks (RR) for females/males, breeds, and breed groups were calculated by dividing the incidence rate of the subgroup of interest by the incidence rate of all other dogs in the study population. The risk of multiple MCT events compared to one MCT event was calculated using the time from the first to second event in dogs affected by multiple events and the time from the first event to censoring (i.e. termination of the insurance or end of the study period) in dogs affected once.

Confidence intervals were generated based on the Poisson distribution using the R package "epitools", which also provided *P* values for intergroup comparisons of incidence rates using exact Poisson tests (Aragon, 2020). Forest plots of breed risks were generated using the "forestplot" package (Gordon and Lumley, 2023). Bonferroni (BF) correction was used to correct for multiple comparisons and was based on the number of comparisons. P-values < 0.05, after correction, were considered statistically significant. A plot for the age-specific incidence rate was generated using the "ggplot2" package, including only the first MCT claim for each affected dog (Wickham, 2016).

A nested case-control study was performed to assess the predisposition to other disorders in dogs with MCT. Each dog with MCT was matched to five control dogs without claims for MCT from the

population of dogs insured for veterinary care, based on age, insurance duration, and breed with nearest neighbour matching on propensity scores using the matchit() function from the package "MatchIt" (Ho et al., 2011). All controls were unique, i.e. no control was included more than once. Information regarding the age, duration of insurance and top breeds among cases and controls is presented in Supplementary Table 2. All veterinary care claims in the cases and controls during the study period were grouped based on the organ system, according to the diagnostic registry (Svenska Djursjukhusföreningen, 1993). Conditional logistic regression using the clogit() function from the "survival" package was used to compare prior and subsequent diagnoses (relative to the first MCT event in cases and the date of matching in controls) (Therneau, 2021). The MCT diagnosis was set as the main exposure variable and the comorbidity as the outcome in the analysis of previous diagnoses, while the MCT diagnosis was set as the main exposure and the comorbidity as the outcome when subsequent diagnoses were analysed. Other diagnoses on the date when MCT was diagnosed were not included in this analysis, but were reported separately for the dogs affected by MCT. Some specific diagnoses (i.e. pruritus, gastritis and/or gastric ulceration, and vomiting/diarrhoea/enteritis, see Supplementary Table 3 for the included diagnostic codes) were chosen as conditions of interest in this study, as paraneoplastic syndromes associated with these signs can affect dogs with MCT. The occurrence of these diagnoses was compared between cases and controls using conditional logistic regression as previously described.

3. Results

3.1. The number of MCT cases and the incidence rate of MCT

The study population included just over 600,000 dogs insured by Agria Djurförsäkring (2011–2016), and 649 dogs were excluded due to missing data. Of the included dogs, 61.8 % were enrolled in both veterinary care and life insurance, while 35.4 % and 2.7 % were enrolled only in veterinary care or life insurance, respectively. There were 949 dogs affected by MCT (i.e. that either had veterinary care claims and/or life insurance settlements due to MCT), of which 521 (54.9 %) were females and 428 (45.1 %) males. Of these, 917 dogs had a total of 1841 veterinary care claims for MCT, and 87 dogs had life insurance settlements related to MCT (Table 1). The median number of veterinary care claims for MCT per affected dog was 1 (IQR 1–2, range 1–40). The incidence rate of MCT was 5.23 (95 % CI: 4.90–5.58) cases per 10,000 DYAR, and the risk of a veterinary care claim for MCT was higher in females than in males (RR 1.29, 95 % CI: 1.13–1.48, $P < 0.001$).

Table 1
Descriptive features of dogs insured by Agria Djurförsäkring in Sweden during 2011–2016.

	Veterinary care insurance	Life insurance
The total duration of insurance (years)	> 1.7 million	> 1.1 million
Insurance duration, median (range)*	2.68 y (9.15 w – 6.00 y)	2.51 y (9.15 w – 6.00 y)
Sex (%)		
Female	49.1 %	49.5 %
Male	50.9 %	50.5 %
Number of dogs with claims for MCT	917	87
Female	508	43
Male	409	44
Age (years) at MCT claim, median (IQR, range)**	7.93 (6.16–9.40, 0.44–15.4)	8.33 (6.50–9.22, 2.16–11.7)

MCT: mast cell tumour, *IQR:* interquartile range
* Per dog, during 2011–2016
** At the first MCT claim during the study period for the veterinary care claims and at life insurance settlement, respectively

3.2. Breed-related risk of MCT

In total, 11 breeds had an increased risk of a veterinary care claim for MCT, and 4 breeds had a decreased risk (relative to the rest of the study population with the breed excluded) after Bonferroni correction (Fig. 1). The breeds at highest risk were the Dogo Argentino (RR 30.0, 95 % CI 9.70–70.2), Boxer (RR 9.78, 95 % CI 7.02–13.3), and Bullmastiff (RR 8.83, 95 % CI 3.54–18.3), while the breeds at lowest risk were the German shepherd dog (RR 0.15, 95 % CI: 0.05–0.35), Jämthund (RR 0.10, 95 % CI 0.01–0.35), and Cavalier King Charles spaniel (RR 0.06, 95 % CI 0.00–0.35). The full list of high- and low-risk breeds without Bonferroni correction is presented in Supplementary Figure 1.

The breed group with the highest risk of MCT (relative to the rest of the study population with the breed group excluded) was breed group 8: retrievers, flushing dogs and water dogs (RR 2.86, 95 % CI 2.48–3.29). Breed group 5, the spitz and primitive types (RR 0.19, 95 % CI 0.11–0.31), had the lowest risk (Fig. 2).

3.3. Age at diagnosis

The median age at first diagnosis (veterinary care claim) of MCT during the study period was 7.93 years (IQR 6.16–9.40, range 0.44–15.4, Table 2) and varied with breed. Breeds older and younger at first diagnosis (relative to the rest of the study population with the breed excluded) are presented in Table 2.

The age-specific incidence rate of veterinary care claims for MCT peaked in dogs aged 8 to < 9 years at 12.2 cases per 10,000 DYAR (Fig. 3).

3.4. Multiple MCT events

In total, 106/917 (11.6 %) of the dogs with veterinary care claims for MCT had two claims at least 3 months apart and were thus considered having multiple MCT events according to the study definition. Dogs with multiple MCT events were younger at first diagnosis (median age 7.33 years, IQR 5.55–8.68, range 2.58–14.5) than dogs with one event (median age 8.02, IQR 6.20–9.50, range 0.44–15.4) (Wilcoxon rank sum test, $P = 0.009$). No breeds had significantly increased or decreased risk of multiple MCT events compared to having one event ($P > 0.05$, exact Poisson test).

3.5. Other diagnoses in dogs with MCT

Of the 917 dogs with veterinary care claims for MCT, 719 (78.4 %) had claims for other diagnoses before the first MCT claim, and 664 (61.7 %) had subsequent claims for other diagnoses. Diagnoses affecting the integumentary (before 62.1 %, after 34.5 %), gastrointestinal (before 21.3 %, after 19.6 %), and urogenital (before 17.3 %, after 15.3 %) systems as well as other/general diagnoses (before 17.6 %, after 19.7 %) were most common both before and after the MCT claim. Dogs with MCT had increased odds of prior diagnoses affecting the gastrointestinal, hematopoietic, integumentary, musculoskeletal, and urogenital organ systems and subsequent diagnoses affecting the gastrointestinal, hematopoietic, integumentary, ophthalmic and urogenital organ systems compared to the controls (n = 4585, Table 3). In addition, the dogs with MCT had increased odds of unspecific/general diagnoses both prior and subsequent to the MCT diagnosis compared to the controls. Further, dogs with MCT had increased odds of a prior diagnosis of vomiting/diarrhoea/enteritis (OR 1.66, $P < 0.001$) and pruritus (OR 2.52, $P < 0.001$) compared to the controls, while no increased odds of gastritis/ventricular ulcus were found (OR 1.58, $P = 0.329$).

In total, 152 (16.6 %) of the dogs with veterinary care claims for MCT had concurrent comorbidities on the same date as their first MCT diagnosis. Integumentary (n = 103, 11.2 %) diagnoses were most common, followed by unspecific/general (n = 24, 2.62 %) and urogenital

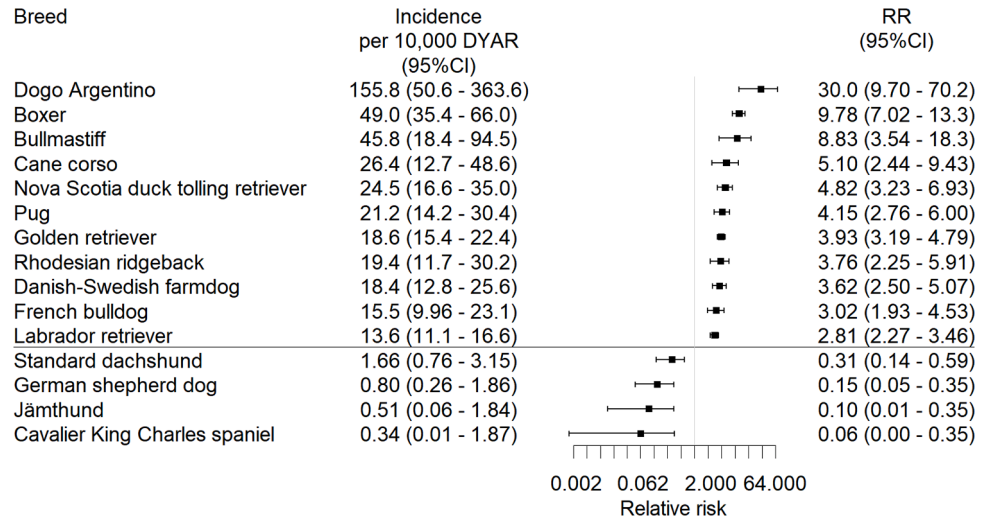

Fig. 1. Dog breeds with an increased or decreased risk of mast cell tumours (relative to the rest of the study population with the breed excluded) in a cohort of dogs insured during 2011–2016 by Agria Djurförsäkring in Sweden. All relative risks (RR) were significantly different from one after the Bonferroni correction based on the number of breeds included in the comparison (n = 339, exact Poisson test).
CI confidence interval, *DYAR* dog-years at risk

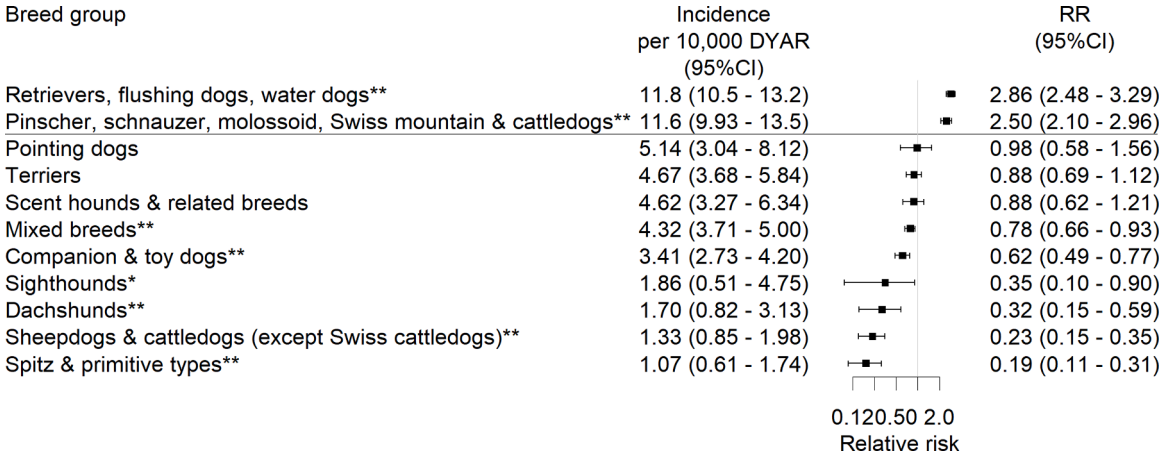

Fig. 2. The risk of mast cell tumours in breed groups (relative to the rest of the study population with the breed group excluded) in a cohort of dogs insured during 2011–2016 by Agria Djurförsäkring in Sweden (exact Poisson test). *breed groups with a relative risk (RR) significantly different from one without Bonferroni. **breed groups with a RR significantly different from one after the Bonferroni correction based on the number of comparisons (n = 11).
CI confidence interval, *DYAR* dog-years at risk

diagnoses (n = 9, 0.98 %). The most common diagnostic codes within the integumentary system were neoplastic disease of the skin and subcutaneous tissue (n = 62) and complications related to surgery or injections (n = 11).

3.6. Mast cell tumour-related death

In total, 87 of the life-insured dogs in the study population died of MCT-related causes during the study period. Of the 917 dogs with veterinary care claims for MCT, 603 (65.8 %) were life insured, and 111 (18.4 %) of those died during the study period. Of these deaths, 55 (49.5 %) were MCT-related. The total cause-specific mortality of MCT was 0.79 (95 % CI: 0.63–0.97) deaths per 10,000 DYAR.

The median time from the first veterinary care claim for MCT to MCT-related death was 54 days (IQR 0.50–166 days, range 0.00 days–2.55 years). No association was found between sex and the risk of MCT-related death (RR 1.01, 95 % CI: 0.65–1.57, $P > 0.999$ in females compared to males).

Nine breeds had an increased risk of MCT-related death compared to the rest of the life-insured population with the breed excluded, of which the Dogo Argentino (RR 55.6, 95 % CI: 1.39–318) and Shar-pei (RR 51.5, 95 % CI: 13.7–137.0) had the highest risk. After Bonferroni correction, significance was lost for all breeds except the Golden retriever (RR 4.40, 95 % CI: 2.24–8.00) and the Shar-pei, due to the low number of cases within each breed. All breeds at high risk of MCT-related death, without Bonferroni correction, are presented in Supplementary Figure 2.

The median age at MCT-related death was 8.33 years (IQR 6.50–9.22, range 2.16–11.7), compared to the age at death in life insured dogs in the study population that died of other reasons during the study period, which was 7.52 years (IQR 4.91–9.14, range 0.19–12.0, Wilcoxon rank-sum test, $P = 0.012$). The Bernese mountain dog was significantly younger than other dogs at MCT-related death, with a median age of 4.29 (IQR 4.15–5.34, range 4.01–6.39) at death ($P < 0.05$, no Bonferroni correction).

Table 2
Breeds significantly older or younger at first diagnosis* of mast cell tumours (MCT) during the study period (2011–2016), in dogs insured by Agria Djurförsäkring in Sweden. The overall median age at first MCT diagnosis was 7.93 years (interquartile range 6.16–9.40, range 0.44–15.4), and each breed was compared to the rest of the dogs in the study population, with the breed excluded.

Breed	Median age at first MCT diagnosis in years (interquartile range, range)
Younger at diagnosis	
Greyhound	3.58 (2.92–4.25, 2.25–4.91)
Shetland sheepdog	4.26 (2.97–5.87, 2.67–7.10)
Bernese mountain dog	5.69 (4.29–7.60, 3.84–8.70)
Giant schnauzer	6.06 (4.78–6.73, 4.06–7.99)
French bulldog	6.51 (4.23–7.96, 1.41–10.2)
Boxer**	6.62 (4.92–8.11, 2.45–9.69)
Pug	6.92 (4.40–8.45, 2.21–11.0)
Golden retriever	7.28 (5.54–8.90, 2.78–12.8)
Older at diagnosis	
Mixed breed	8.38 (6.83–9.87, 0.90–13.6)
Parson Russell terrier	9.94 (9.56–10.5, 9.24–11.6)
Standard poodle	9.97 (9.59–11.0, 8.42–12.6)
Miniature schnauzer	10.4 (8.92–11.0, 6.27–12.5)
Standard dachshund	10.4 (9.42–12.0, 5.54–15.3)
Cairn terrier**	11.2 (9.64–11.9, 8.48–13.8)

* Evaluated using Wilcoxon rank sum test, $P < 0.05$ without Bonferroni correction for all breeds included in the table

** In these breeds, age differed significantly from all other breeds after Bonferroni correction based on the number of comparisons, n = 109 (i.e. number of breeds with veterinary care claims for MCT)

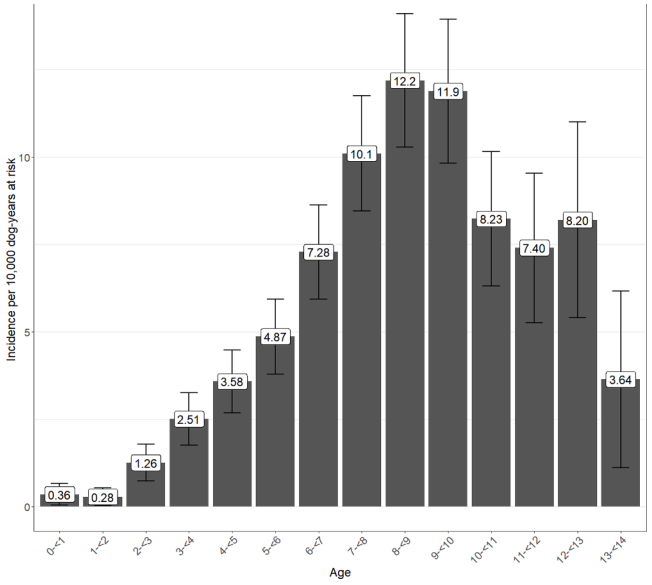

Fig. 3. The age-specific incidence rate of mast cell tumours in dogs insured by Agria Djurförsäkring in Sweden, 2011–2016.

4. Discussion

This study aimed at exploring the epidemiology of MCT in an insured Swedish dog population and found an incidence of 5.23 cases per 10,000 DYAR. Previous estimates of the incidence of MCT in the literature are few; Dobson et al. (2002) reported 12.9 cases per 10,000 dogs per year using data on insured dogs in the UK 1997–1998, and Graf et al. (2018) 6.03 cases per 10,000 dogs per year using data from the Swiss canine cancer registry 2008–2013. It should be noted that our results are not directly comparable to those by Dobson et al. (2002) and Graf et al. (2018) due to differences in study design and measures of disease occurrence (DYAR vs. dogs per year).

Females had a higher risk of MCT compared to males (RR 1.29), in concordance with the results from Smiech et al. (2018), who reported an odds ratio of 1.38 in females compared to males. On the contrary, no sex predisposition was observed in most other studies evaluating the association between sex and MCT (Baker-Gabb et al., 2003; Welle et al., 2008; Shoop et al., 2015; Gruntzig et al., 2016). The role of sex hormones in MCT oncogenesis is not fully understood, and the discussion regarding the impact of sex hormones on MCT development has mostly focused on the association between neutering and the risk of MCT (Zink et al., 2014; Smiech et al., 2018; Pierini et al., 2019; Martins et al., 2021). This association has been evaluated in several studies, for example by Shoop et al. (2015), who reported lower odds of MCT in neutered dogs. In contrast, White et al. (2011) reported increased odds in neutered compared to intact females, and Gruntzig et al. (2016) reported increased odds in neutered females and males compared to intact. The current study lacked information regarding neutering, but in general, a relatively low proportion of Swedish dogs were neutered during the study period (neuter prevalence 22.3 % ± 4.8 in 2012 (Statistics Sweden, 2012)). Although recent estimates are lacking, a higher percentage of neutered females than males in the Swedish dog population has been reported previously, which potentially affected the association between sex and MCT in the current study (Egenvall et al., 1999).

The breeds at highest risk of MCT (Dogo Argentino, Boxer, Bullmastiff and Cane corso) were of molossoid/mastiff type, belonging to breed group two, which also had an increased risk of MCT in general ("Pinscher, schnauzers, molossoid, Swiss mountain & cattledogs"). There were also two breeds of small molossian type, the Pug and French bulldog, among the high-risk breeds. A high risk of MCT in the phylogenetic cluster for mastiffs and terriers has been identified previously, suggesting that these breeds may share features that increase the risk of MCT development (White et al., 2011). Further, Peters (1969) suggested already over 50 years ago that a strong relationship to the bulldog or English terrier could cause an increased breed susceptibility to MCT.

Breed group 8, including retrievers, flushing dogs, and water dogs, also had an increased risk of MCT in the current study, in concordance with the results from Gruntzig et al. (2016) reporting an increased risk of MCT in Retrievers. High-risk breeds in this breed group included the Nova Scotia duck tolling retriever (RR 4.82), Golden retriever (RR 3.93), and Labrador retriever (RR 2.81), of which the Golden and Labrador retrievers are reported as high-risk breeds in several previous studies (Villamil et al., 2011; White et al., 2011; Warland and Dobson, 2013; Pierini et al., 2019).

The fact that strong breed predisposition exists suggests a genetic component to the disease aetiology, and the genetic background of MCT has been explored previously (Vozdova et al., 2020; Zmorzynski et al., 2024). For example, a synonymous variant in the DSCAM gene on canine chromosome 31, encoding a cell-adhesion molecule, has been suggested to be a significant genetic contributor to MCT development in Golden and Labrador retrievers (Biasoli et al., 2019). In another study on Golden retrievers, changes in different hyaluronidase genes were associated with MCT risk, which suggests that hyaluronan (HA) could have an important role in MCT development (Arendt et al., 2015). The binding of HA to CD44 (a primary receptor for HA) has been reported to be involved in the regulation of cutaneous and connective tissue mast cell proliferation in rodents and could potentially influence local immune responses by regulating mast cell activity (Takano et al., 2009; Tanaka, 2010). The Shar-pei, commonly reported at high risk of MCT, has up-regulation of HA associated with the thick skin of the breed, which has been suggested to contribute to the susceptibility of mast cell disease and allergic skin disease in the breed (Olsson et al., 2011; Villamil et al., 2011; White et al., 2011). However, the genetic background of MCT is still not fully understood (White et al., 2011) and should be explored further in future studies, preferably in molossoid breeds given their identified predisposition. All identified low-risk breeds in the current

Table 3
Prior and subsequent diagnoses* by organ system in dogs with mast cell tumours (n = 917) and controls without veterinary care claims for mast cell tumours (n = 4585) matched on age, breed, and duration of veterinary care insurance in a cohort of dogs insured for veterinary care by Agria Djurförsäkring in Sweden (2011–2016). Significant *P*-values (after Bonferroni correction) are in bold and indicate that dogs with MCT have an increased risk of a diagnosis compared to dogs without MCT.**

	Prior diagnoses				Subsequent diagnoses			
Organ system	Cases (%)	Controls (%)	Odds ratio	*P*-value***	Cases (%)	Controls (%)	Odds ratio	*P*-value***
Cardiovascular	13 (1.42)	53 (1.16)	1.23	0.503	25 (2.73)	73 (1.59)	1.72	0.020
Endocrine	18 (1.96)	50 (1.09)	1.82	0.031	19 (2.07)	61 (1.33)	1.57	0.089
Gastrointestinal	195 (21.3)	582 (12.7)	1.89	<0.001	180 (19.6)	540 (11.8)	1.82	<0.001
Hematopoietic	19 (2.07)	34 (0.74)	2.79	<0.001	34 (3.71)	90 (1.96)	1.91	0.001
Hepatic	11 (1.20)	51 (1.11)	1.08	0.820	24 (2.62)	98 (2.14)	1.24	0.362
Integumentary	569 (62.1)	926 (20.2)	6.92	<0.001	316 (34.5)	713 (15.6)	2.85	<0.001
Musculoskeletal	148 (16.1)	479 (10.5)	1.67	<0.001	124 (13.5)	475 (10.4)	1.36	0.005
Neurologic	16 (1.74)	100 (2.18)	0.79	0.400	29 (3.16)	132 (2.88)	1.10	0.641
Ophthalmic	65 (7.09)	220 (4.80)	1.51	0.005	65 (7.09)	193 (4.21)	1.74	<0.001
Other (general/unspecific)	161 (17.6)	453 (9.88)	1.98	<0.001	181 (19.7)	542 (11.8)	1.85	<0.001
Respiratory	33 (3.60)	119 (2.60)	1.40	0.092	30 (3.27)	160 (3.49)	0.94	0.742
Urogenital	159 (17.3)	515 (11.2)	1.69	<0.001	140 (15.3)	501 (10.9)	1.49	<0.001
Any diagnosis	719 (78.4)	1921 (41.9)	5.44	<0.001	566 (61.7)	1959 (42.7)	2.18	<0.001

*Relative to the first veterinary care claim for mast cell tumours during the study period or the date of matching for the controls.
***P*-values were generated using conditional logistic regression
**Significance level 0.05/13 (number of comparisons of prior and subsequent diagnoses) = 0.004

study, except for the Jämthund, a Swedish spitz commonly used for hunting, have been reported as low-risk breeds in previous studies (Villamil et al., 2011; Warland and Dobson, 2013; Shoop et al., 2015; Gruntzig et al., 2016; Aupperle-Lellbach et al., 2022; Rodriguez et al., 2023; Svenska Kennelklubben, 2024b). The reason for protection from MCT in these breeds is yet to be explored.

The median age at first MCT diagnosis was 7.93 years, which is within the interval of 7–9 years reported previously (Patnaik et al., 1984; Baker-Gabb et al., 2003; Welle et al., 2008; Kiupel et al., 2011; Shoop et al., 2015). The odds of diagnosis are reported to increase with age (Villamil et al., 2011; Shoop et al., 2015), a trend that was noted in the current study too. Mochizuki et al. (2017) found a tendency to develop MCT at a younger age in breeds of Bulldog origin, such as the Boxer, French bulldog, American Staffordshire terrier, Staffordshire bull terrier, and Boston terrier, and Miller (1995) reported a low age at MCT diagnosis in the Shar-pei. Some of these breeds were among the breeds younger at diagnosis in the current study, together with the Greyhound, Shetland sheepdog, Bernese mountain dog, Giant schnauzer, Pug, and Golden retriever. The grade of malignancy tends to increase with age (Mochizuki et al., 2017). Further, several breeds of Bulldog origin and Pugs are reported to have a relatively larger proportion of low- and intermediate compared to high-grade tumours than other breeds, which might have contributed to their lower age at diagnosis in this study (McNiel et al., 2006; Mochizuki et al., 2017). However, the association between age at diagnosis and malignancy of the tumour could not be evaluated in the current study, as information regarding the grade of malignancy was lacking. Small- and medium-sized breeds tend to develop MCT at an older age (Mochizuki et al., 2017), which is in line with our results. This could be influenced by the generally longer longevity of smaller breeds compared to larger (O'Neill et al., 2013)

The median time to recurrence in dogs with MCT has been reported to be 3 months, although this estimate was based on only a few dogs (Baker-Gabb et al., 2003). In the current study, 11.6 % of the dogs with MCT had two claims at least 3 months apart and were thus considered having multiple MCT events. However, it could not be verified if this was due to local recurrence, a new tumour, or prolonged treatment of the initial tumour. Between 5 % and 25 % of dogs with MCT are reported to be affected by multiple MCT, appearing at the same time or sequentially, and about the same rate of dogs develop local recurrence after initial treatment (5–23 %) (London and Seguin, 2003; Murphy et al., 2006; Welle et al., 2008; Pierini et al., 2019). Boxers and Golden retrievers are reported to have an increased risk of developing subsequent MCTs at distant sites and having multiple MCTs, respectively (Kiupel et al., 2005; Murphy et al., 2006). The current study found no association between breed and having multiple MCT events. However, the number of dogs with multiple events was relatively low (n = 106), yielding a low number of dogs in each affected breed, increasing the risk of type II errors in the analysis. Further, the occurrence of multiple MCTs at the same time could not be evaluated.

Paraneoplastic signs occur in dogs with MCT and are related to mast cell degranulation and the release of histamine, heparin, eosinophilic chemotactic factor and proteolytic enzymes (Welle et al., 2008; de Nardi et al., 2022). Gastrointestinal paraneoplastic syndrome is reported to be common: a study based on data from medical records described that approximately 40 % of dogs with cutaneous MCT were affected by reduced appetite, vomiting, abdominal pain, and/or diarrhoea (Ledur et al., 2023). In the current study, the percentage of dogs with gastrointestinal signs preceding the MCT diagnosis was lower (21.3 %). It is important to note that these signs may have appeared at any time prior to the MCT diagnosis. Thus, it was not possible to determine whether they occurred before or concurrently with the MCT or to what extent they represented paraneoplastic signs. Increased odds of a previous diagnosis of vomiting/diarrhoea/enteritis (OR 1.66) were identified, supporting that dogs with MCT are at increased risk of these signs, regardless of whether these represented paraneoplastic signs or not. It cannot be excluded that some owners, in this case, the owners of dogs affected by MCT, are more likely to seek veterinary care for their pets, which potentially influenced these results. Increased odds of a previous diagnosis of pruritus were also identified, and 62.1 % of the dogs with MCT were diagnosed with disorders affecting the integumentary system at some point before the MCT diagnosis. Thus, gastrointestinal and integumentary signs are common in dogs with MCT, but whether these reflected paraneoplastic clinical signs or not could not be verified in the current setting.

In total, 87 dogs died of MCT-related causes in the current study. Of the dogs with veterinary care claims for MCT that were life insured, 9.12 % died of MCT-related causes. This is lower than in the study by Patnaik et al. (1984), reporting that 45.8 % of the dogs with MCT had died due to MCT 1500 days post-surgery. Variations in the duration of the follow-up period could have led to disparate outcomes. Further, the prognosis and survival of dogs with MCT are significantly influenced by tumour grade and differentiation, which may have impacted the findings (Bostock, 1973, 1986). For example, Murphy et al. (2004) reported that 64 % of the dogs with poorly differentiated MCT died because of MCT, while only 13 % of the dogs with intermediate differentiated tumours and none of the dogs with well-differentiated tumours died. In

general, factors that negatively affect the prognosis in dogs with MCT include tumour location, tumours appearance (local ulceration, erythema, pruritus, a high growth rate, tumour size), systemic paraneoplastic signs, a higher clinical stage, metastasis at diagnosis, lymph node involvement, and postsurgical recurrence (Bostock, 1986; Welle et al., 2008; Pierini et al., 2019). However, the exact cause of MCT-related death could not be evaluated in the current study.

The median time from the first veterinary care claim for MCT during the study period to MCT-related death was only 54 days, which is shorter than the 12-month median survival time in dogs that died due to MCT in the study by Baker-Gabb et al. (2003). The inclusion of all dogs with MCT (and not only surgically treated dogs as in the study by Baker-Gabb et al. (2003) likely affected these results, as some of the included dogs might have been euthanised at or close to the time of diagnosis for factors such as a high age at diagnosis, comorbidities, or a perceived guarded prognosis. Dogs that died/were euthanised due to MCT lived longer on average than dogs that died of other reasons (8.33 vs. 7.52 years). This was likely influenced by the fact that the median age at MCT diagnosis was 7.93 years, i.e. higher than the age at death of other reasons, despite the median time from first diagnosis to MCT-related death being relatively short.

There were breeds of all sizes in the full list of breeds at high risk of MCT-related death. As a high tumour grade is associated with a higher mortality, the grade of the tumour might have influenced the association between breed and the risk of MCT-related death (Patnaik et al., 1984). Increased odds/occurrence of high-grade MCT have been reported in the American Staffordshire terrier, Bernese mountain dog, and the Shar-pei (Miller, 1995; Mochizuki et al., 2017; Smiech et al., 2018, 2019; Reynolds et al., 2019), which all were on the full list of breeds at high-risk of MCT-related death in the current study. In contrast, the Boxer, Bullmastiff, French bulldog, Rhodesian ridgeback, Labrador retriever, and Pug had an increased risk of MCT diagnosis but not an increased risk of MCT-related death (compared to all other breeds in the study population, with the breed excluded). This is in line with previous research, reporting a higher survival rate in Boxers and Pugs due to their high occurrence of well-differentiated tumours (Bostock, 1973, 1986; McNiel et al., 2006). Associations between the grade of the tumour and MCT-related death could not be evaluated in the current study, but the fact that some breeds had an increased risk of MCT-related death highlights the importance of examining skin tumours in these breeds extra carefully.

This study was performed on insurance data, and some important aspects should be considered. An effect of using insurance data compared to laboratory histopathological data is the potential inclusion of MCT cases diagnosed by the examining veterinarian by cytology (which is reported to yield a correct diagnosis in 96 % of cases (Baker-Gabb et al., 2003)) without the involvement of a histopathological laboratory. Thus, the dogs with MCT in this study may better represent the typical population of dogs affected by MCT. As previously mentioned, histopathological data, including grading of the tumours, would have been useful but were unavailable.

The insurance data depend on the reporting by the examining veterinarians and dog owners. There is a risk that the cost associated with the veterinary examination in dogs with MCT treated non-surgically did not reach the deductible limit of the insurance. This risk should be low, as the cost of a veterinary examination and a cytological examination generally exceeds most pet insurance deductibles. However, some MCTs might have been missed if no cytological assessment was performed, but this situation is not unique in studies using insurance data. There is a risk of underestimation of the cause-specific mortality and the age at MCT-related death, as the life insurance terminated at 8/10/12 years of age (depending on breed). Further, some cases where MCT contributed to death/euthanasia might have been registered under other diagnostic codes, as the cause of death can be multifactorial. Such cases could not be included when the cause-specific mortality was assessed.

The Agria Djurförsäkring database was validated against practice records > 20 years ago, showing excellent agreement for sex and breed but a fair agreement for birth date (Egenvall et al., 1998). Clinics with computerised medical records showed a tendency towards better agreement and thus, the current agreement is likely better since computerised medical records are used in most Swedish clinics. Access to the medical records of the included dogs was not possible due to GDPR, even though validation of the diagnoses against medical records would have been desirable. Thus, information regarding the diagnostic work-up, treatment and outcome (other than death) was unavailable. The database used in the current study was large, generally resulting in high power in statistical calculations (Egenvall et al., 2009). Thus, relatively small inter-group differences can be identified as statistically significant, and the magnitude of the difference and the potential clinical relevance have to be considered when results are interpreted. Further, calculations based on smaller subgroups, such as disease risk estimation in uncommon breeds, might be less statistically powered, and the width of the confidence intervals should be considered when the precision of the estimates is evaluated.

Some aspects should be considered regarding the generalisation of the results to other dog populations. Uninsured dogs might differ from insured ones: previous research has shown that mixed breeds are insured to a lesser degree than purebred dogs in Sweden, but recent comparisons of the insured vs. uninsured dog populations in Sweden are lacking (Egenvall et al., 1999). Higher odds of MCT in insured compared to non-insured dogs have been reported, potentially linked to further testing that confirms the MCT in insured dogs (Shoop et al., 2015). In Sweden, around 90 % of the dog population is insured, but the generalisability to dog populations in other countries with less insurance coverage might be limited (Agria Djurförsäkring, 2017). Further, international differences in breed popularity might also impact generalisability.

5. Conclusion

In total, 917 dogs had veterinary care claims for MCT during the study period. The incidence of MCT was 5.23 cases per 10,000 DYAR and peaked in dogs 8 to < 9 years old. Large breed-related differences in the risk of MCT were found, and the breeds at highest risk of MCT were the Dogo Argentino (RR 30.0, 95 % CI 9.70–70.2), Boxer (RR 9.78, 95 % CI: 7.02–13.3), and Bullmastiff (RR 8.83, 95 % CI: 3.53–18.3). The breeds at lowest risk were the German shepherd dog (RR 0.15, 95 % CI: 0.05–0.35), Jämthund (RR 0.10, 95 % CI: 0.01–0.35), and Cavalier King Charles spaniel (RR 0.06, 95 % CI: 0.00–0.35). The majority of the high-risk breeds (6/11) were of molossian/mastiff or small molossian type. The overall median age at MCT diagnosis was 7.93 years, and the Greyhound (3.58 years) and Shetland sheepdog (4.26 years) were youngest at diagnosis, while the Standard dachshund (10.4 years) and Cairn terrier (11.2 years) were oldest. Dogs with MCT had increased odds of a prior diagnosis of vomiting/diarrhoea/enteritis (OR 1.66) and pruritus (OR 2.52) compared to controls. In total, 87 dogs died of MCT-related causes during the study period, and the median age at MCT-related death was 8.33 years, compared to the median age at death of other causes, which was 7.52 years. Of the 603 dogs with veterinary care claims for MCT that also were life-insured, 9.12 % died of MCT-related causes during the study period. The Shar-pei (RR 51.5, 95 % CI: 13.7–137.0) and Golden retriever (RR 4.40, 95 % CI: 2.24–8.00) had an increased risk of MCT-related death. The results can aid veterinarians in advising dog owners regarding the risk of MCT, impact decision-making in clinical practice and assist research on the genetic background of MCT by identification of high- and low-risk breeds.

Authors' contributions

All authors contributed to the study design. K.E. analysed the data and drafted the manuscript with input from all co-authors. All authors participated in the discussions and revisions of the entire text. All

authors read and approved the final manuscript.

CRediT authorship contribution statement

Henrik Rönnberg: Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Åke Hedhammar:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Maria Dimopoulou:** Writing – review & editing, Methodology, Conceptualization. **Karolina Engdahl:** Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Sara Saellström:** Writing – review & editing, Supervision, Methodology.

Funding

K.E. was funded by a grant from the Agria Djurförsäkring and SKK Research Fund in Sweden. The research fund had no impact on the interpretation or presentation of the results.

Declaration of Competing Interest

None.

Acknowledgements

The data access and support from Agria Djurförsäkring is gratefully acknowledged. We would like to thank Monica Dreijer and Lotta Möller for support with data processing, and Ulf Emanuelson and Pekka Olson for support and discussion.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.prevetmed.2025.106589.

Availability of data and materials

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

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