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JOURNAL TITLE: Veterinary Record

PUBLISHER: BMJ Publishing Group

PUBLICATION DATE: 27 August 2018 (online)

DOI: http://dx.doi.org/10.1136/vr.104891

Signalment risk factors for cutaneous and renal glomerular vasculopathy (Alabama Rot) in dogs in the UK

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Abstract

Seasonal outbreaks of cutaneous and renal glomerular vasculopathy (CRGV) have been reported annually in UK dogs since 2012 yet aetiology of the disease remains unknown. The objectives of this study were to explore whether any breeds had an increased or decreased risk of being diagnosed with CRGV, and to report on age and sex distributions of CRGV cases occurring in the UK. Multivariable logistic regression was used to compare 101 dogs diagnosed with CRGV between November 2012 and May 2017 with a denominator population of 446 453 dogs from the VetCompass™ database. Two Kennel Club breed-groups – hounds (OR 10.68) and gundogs (OR 9.69) – had the highest risk of being diagnosed with CRGV compared with terriers, while toy dogs were absent from among CRGV cases. Females were more likely to be diagnosed with CRGV (OR 1.51) as were neutered dogs (OR 3.36). As well as helping veterinarians develop an index of suspicion for the disease, better understanding of the signalment risk factors may assist in the development of causal models for CRGV and help identify the aetiology of the disease.

Keywords: *Acute kidney injury; Alabama Rot; CRGV; cutaneous and renal glomerular vasculopathy; epidemiology; Kennel Club breed-groups; signalment; risk factors; VetCompass*

Introduction

Cutaneous and renal glomerular vasculopathy (CRGV) is a disease of unknown aetiology variably associated with clinically relevant acute kidney injury (AKI). Also sometimes referred to as 'Alabama Rot', CRGV cases typically present with ulcerated skin lesions, most often affecting the distal limbs, although lesions have also been reported to affect the face, nasal planum, oral cavity, tongue, ventrum and flanks. Common biochemical and haematological features have included mild to moderate hyperbilirubinaemia, anaemia and moderate to severe thrombocytopenia (Holm and others 2015).

A previous case series (Holm and others 2015) indicated that cases presenting with skin ulceration typically progress within a range of 1-9 days (median 4 days) to develop AKI, azotaemia and in many confirmed cases, acute renal failure with oligo-anuria. Mortality rate in those cases that progress to oligo-anuria is high with a confirmatory diagnosis of CRGV only being made at post-mortem examination. However, suspected cases have been identified that appear less severely affected and where renal recovery may occur, although lack of a viable ante-mortem diagnostic test precludes definitive diagnosis in these cases.

The histopathological lesions identified in the renal parenchyma of CRGV patients are supportive of a thrombotic microangiopathy (TMA) (Holm and others 2015). In human medicine, TMAs are considered a complex group of diseases which can involve both hereditary and acquired contributing factors to the development of clinical disease (George and Nester 2014). Hereditary factors that have been identified include genetic mutations in ADAMTS13, which results in the condition known as thrombotic thrombocytopenic purpura (TTP), complement factors, metabolic factors (MMACHC; methyl-malonic aciduria and homocystinuria type C protein) and diacylglycerol kinase-ε (DKGE), an abnormality of which results in a prothrombotic state. Acquired forms of TMA may be associated with autoantibody inhibition of ADAMTS13, shiga toxin exposure (shiga toxin-haemolytic uraemic syndrome (STEC-HUS), drug-mediated immune or toxic reactions, or complement mediated (George and Nester 2014). To date however, preliminary investigations, including evaluation for shiga-toxin (Holm and others 2015) and other infectious aetiologies, have not been able to elucidate an underlying aetiology for CRGV and therefore epidemiological studies are required to better understand risk factors that may indicate pathogenesis in this condition.

CRGV has been reported in kenneled and racing greyhounds in the USA (n = 168 (Carpenter and others 1988); n = 18 (Cowan and others 1997)), a single greyhound in the UK (Hendricks 2000) and in a Great Dane in Germany (Rotermund and others 2002). In contrast to these few isolated incidents the UK outbreaks have involved multiple breeds including the English Springer Spaniel, Flat-Coated Retriever, Whippet, Border Collie, Jack Russell Terrier, Doberman, Labrador Retriever, Cocker Spaniel, Staffordshire Bull Terrier, Hungarian Vizsla, Weimaraner, Dalmatian, Tibetan Terrier and crossbreds (Holm and others 2015). The objectives of this study were therefore to explore whether any breeds had an increased or decreased risk of diagnosis with CRGV, and to report on the age and sex distributions of CRGV cases occurring in the UK. These results may assist with validation of current and future proposed pathogenic mechanisms and also assist clinicians to develop their index of suspicion achieve earlier diagnosis of this serious condition.

Materials and methods

Study area, period and design

This research was based on a retrospective case-control study involving dogs with a confirmed diagnosis of CRGV in the UK between November 2012 and May 2017 (103 cases). The denominator population comprised all dogs under veterinary care in the UK during 2013 that were participating in the VetCompassTM programme and that are taken to represent the demography of the wider population of UK dogs that are registered for veterinary care from which the cases were derived. Because the cases were not extracted directly from the denominator population, this case-control study design cannot reliably report the incidence of CRGV but can usefully explore risk factor analysis (Dohoo and others 2009).

Identification of cases

Cases were compiled by two investigators (DW & LH) with 70 (68 %) from first-opinion practice and 33 (32 %) from referral centres. A confirmed diagnosis of CRGV was based on the presence of compatible clinical signs (including skin lesions), laboratory diagnostics (including progression to azotaemia, AKI +/- oligo-anuria, hyperbilirubinaemia, anaemia and thrombocytopenia) and renal histopathology documenting findings compatible with thrombotic microangiopathy. Renal histopathology was available either in isolation or as part of a full post-mortem examination, and in most cases dermal pathology was also available. The need for renal histopathology to confirm diagnosis precluded the inclusion of any dogs surviving suspected CRGV.

Identification of dog denominator data

The ‘VetCompass™ Denominator of Dogs under Veterinary Care in the UK during 2013’ [aka dog denominator] population included all dogs under primary veterinary care at clinics participating in the VetCompass™ Programme during 2013. Dogs under veterinary care were defined as those with either a) at least one electronic patient record [EPR] (VeNom diagnosis term, free-text clinical note, treatment or bodyweight) recorded during 2013 or b) at least one EPR recorded both before and after 2013. The VetCompass™ Programme collates de-identified EPR data from primary-care veterinary practices in the UK for epidemiological research (VetCompass 2017). Collaborating practices can record summary diagnosis terms during episodes of care from an embedded VeNom Code list (The VeNom Coding Group 2017).

Data fields extracted from the VetCompass™ dataset for the purpose of this study included a unique animal identifier together with (where available) breed, date of birth, sex, neuter status and partial postcode. The breed data recorded in the EPR were mapped to a standardized listing of breed terms. These breed lists were further mapped to classify breeds by purebred status, Kennel Club (KC) recognition of the breed and KC breed-group. Neuter status described the status of the dog at the final EPR while age was calculated from date of birth and described age at the final date under veterinary care during 2013 (December 31st, 2013). Signalment and partial postcode of all cases were compared to the denominator dogs to ensure that none of the cases were duplicated as controls.

Statistical analyses

The CRGV case and dog denominator control datasets were combined to form the final dataset which was checked for unlikely values and missing data. Observations with missing data for three variables were removed from the dataset as follows: breed (0.4 % of controls (n = 2009); no cases), sex (0.5 % of controls (n = 2310); no cases) and age (1.4% of controls (n = 6117); 1.9 % of cases (n = 2)). However, of the 72 344 observations that lacked data on neutered status, 15 (15 %) were CRGV dogs. Rather than lose a quarter of the case data, the missing observations were labelled as 'not recorded' thus creating a neutering status variable comprising three levels: male, female and not recorded. Three variables were derived from breed and included (1) common breed name, (2) purebred versus crossbred versus designer dog (i.e. a planned hybrid with a specific hybrid name e.g. Cockapoo (Oliver and Gould 2012)) and (3) the UK KC breed-groups: hounds, terriers, gundogs, working, utility, pastoral, toy and not KC-recognised.

Descriptive statistics were derived for all variables for both the study population as a whole, and separately for CRGV dogs and the dog denominator population. Univariable logistic regression modelling was used to evaluate associations between each variable and being a CRGV case, together with unadjusted odds ratios and 95 % confidence intervals. The 'common breed' variable included only those breed types that appeared among the CRGV cases. Crossbred and terrier were chosen as the reference values for common breed and breed-group respectively as both were large categories. Age was categorised into four groups based on quartiles to create the variable age-group and a test for linear trend was used to determine whether the variable age should be included in the model in continuous (age) or categorical (age-group) format. Those variables achieving a univariable p-value < 0.2 were taken forward for multivariable logistic regression modelling. Retention of variables in the final model was determined using a backward stepwise approach based on the likelihood ratio test (LRT). Model fit was assessed using Akaike's information criteria (AIC). All statistical analyses were performed in STATA SE 14 and a p-value of $\leq$ 0.05 was considered significant.

Results

Description of study population

The 446 554 dogs comprising the study population had a median age of 4.4 (interquartile range (IQR): 5.90 years; range 0.1 to 24.7 years) and 51.8 % were male (n = 231 450). Neutered dogs comprised 45.5 % (n = 203 313) of the study population, 38.4 % (n = 171 493) were entire and the status of 16.1 % (n = 71 748) was not recorded. Three-quarters of the study population were purebreds (75.2 %; n = 335 807) while 3.0 % were designer dogs (n = 13 602). The most common KC breed-groups were gundogs (16.1 %; n = 72 105), terriers (13.1 %; n = 58 362) and toy dogs (12.6 %; n = 56 431), while working dogs (4.9 %; n = 22 001) and hounds (3.5%; n = 15 646) were the least represented.

Crossbreds were the most common breed-type comprising 37.7 % (n = 97 146) of the study population, with Labrador Retrievers (12.8 %, n = 32 938), Staffordshire Bull Terriers (12.5 %, n = 32 134) and Jack Russell Terriers (10.6 %, n = 27 356) the most common specified breeds. Other relatively common breeds in the study population included Cocker Spaniels (6.1 %, n = 15 671), German Shepherd Dogs (4.8 %, n = 12 321) and Border Collies (4.7 %, n = 12 165). Of those breeds represented among the cases, the least common were Hungarian Vizslas (0.3 %; n = 775), Flat-Coated Retrievers (0.2 %, n = 452), Bearded Collies (0.2 %, n = 538), Salukis (0.1 %, n = 201) and Manchester Terriers (0.05 %, n = 126).

Distributions of breed, age, sex and neuter status of CRGV and denominator dogs

Following removal of missing data, the study population included 101 CRGV case dogs and 446 453 VetCompass™ denominator control dogs. The median age for CRGV dogs (4.0 years (IQR: 4.8 years; range 0.5-12 years) did not differ significantly from the denominator dog population (4.12 years range 0.1-24.7 years; p = 0.874). Compared to the denominator dogs which were evenly distributed between the four age-groups, 34.7 % (n = 35) of the CRGV dogs were aged between 1.73 and 4.11 years old. The smallest group of CRGV dogs comprised those aged less than 1.72 years old (15.8 %; n = 16; p = 0.010). CRGV dogs were more likely to be female (58.4 %; n = 59) compared to denominator dogs (48.2 %; n = 215 045; p = 0.010). Similarly, CRGV dogs were more likely to be neutered (69.3 %; n = 70) compared to denominator dogs (45.5 %; n = 203 243; p < 0.001). Proportions of purebred, designer and crossbred dogs were generally comparable between CRGV and denominator dogs (p = 0.587) (Table 1).

Two KC breed-groups – gundogs and hounds – comprised 60.4 % (n = 61) of the CRGV cases. However, while gundogs were the largest KC breed-group for both CRGV and denominator dogs, proportions differed considerably (48.5 versus 16.1 % respectively; p < 0.001). Likewise, hounds made up a far greater proportion of CRGV dogs than denominator dogs (11.9 versus 3.5 % respectively; p < 0.001). Conversely, terriers were under-represented among CRGV dogs (CRGV: 4.0

%; denominator: 13.1 %) and, despite comprising 12.6 % of denominator dogs ($n = 56\ 431$) there were no toy dogs among those diagnosed with CRGV (Table 1).

Of the five most common specified breeds in the study population (Labrador Retriever, Staffordshire Bull Terrier, Jack Russell Terrier, Cocker Spaniel and German Shepherd Dog) three were under-represented among CRGV dogs: Staffordshire Bull Terriers (3.0 %, $n = 3$ versus 12.5 %, $n = 32\ 131$, $p = 0.201$), Jack Russell Terriers (2.0 %, $n = 2$ versus 10.6 %, $n = 27\ 354$; $p = 0.163$) and German Shepherd Dogs (1.0 %, $n = 1$ versus 4.8 %, $n = 12\ 320$; $p = 0.364$). Conversely, breeds that were over-represented among CRGV dogs were generally the less common breeds such as English Springer Spaniels (10.9 %, $n = 11$ versus 2.1 %, $n = 5337$; $p < 0.001$), Whippets (8.9 %, $n = 9$ versus 0.8 %, $n = 2126$; $p < 0.001$), Flat-Coated Retrievers (6.9 %, $n = 7$ versus 0.2 %, $n = 445$; $p < 0.001$) and Hungarian Vizslas (5.9 %, $n = 7$ versus 0.3 %, $n = 769$; $p < 0.001$) (Table 1).

Common breed ($p < 0.001$), KC breed-group ($p < 0.001$), neutered status ($p < 0.001$), age-group ($p = 0.017$) and sex ($p = 0.010$) were significantly associated with being a CRGV case in the univariable modelling. Owing to collinearity between the derived breed variables, two multivariable models were built, one including common breed and the other including KC breed-group, while keeping the remaining variables constant. Although the use of KC breed-groups resulted in more robust ORs and 95% confidence intervals than when common breeds were used - because there were fewer categories and therefore more dogs in each - the use of specific breeds was considered more useful for veterinarians and therefore the results of both models were presented. In addition, age-group was not a significant risk factor in the multivariable models (LRT $p = 0.06$).

The odds of gundogs (OR 9.69; 3.50 – 28.86; $p < 0.001$) and hounds (OR 10.68; 95 % CI 3.44 – 33.13; $p < 0.001$) being a CRGV case was between 9 and 11 times that of terriers. Pastoral dogs were also significantly more likely to be a CRGV case than terriers (OR 3.50; 95 % CI 1.01 – 11.96; $p = 0.046$). As there were no toy dogs among CRGV cases, this breed-group was dropped from the model**.** Specific breeds with increased odds of being a CRGV case compared with crossbreds included the Flat-Coated Retriever (OR 84.48; 95 % CI 35.19 – 202.80; $p < 0.001$), Hungarian Vizsla (OR 40.98; 95 % CI 16.34 – 102.75; $p < 0.001$), Manchester Terrier (OR 41.41; 95 % CI 5.49 – 312.22; $p < 0.001$), Saluki (OR 27.46; 95 % CI; 3.65 – 206.32; $p = 0.001$), Whippet (OR 22.43; 95 % CI 10.18 – 49.42; $p < 0.001$), English Springer Spaniel (OR 11.41; 95 % CI 5.44 – 23.94; $p < 0.001$) and Bearded Collie (OR 10.85; 95 % CI 1.45 – 81.34; $p = 0.020$). Breeds with decreased odds of being a CRGV case compared with crossbreds were the Staffordshire Bull Terrier (OR 0.50; 95 % CI 0.15 – 1.70; $p = 0.268$), German Shepherd Dog (OR 0.45; 95 % CI 0.06 – 3.38; $p = 440$) and Jack Russell Terrier (OR 0.37; 95 % CI 0.09 – 1.58; $p = 0.179$) (Table 2).

Female dogs were significantly more likely to be a case than male dogs (OR 1.51, 95 % CI 1.02 – 2.24; p = 0.042), while the odds of neutered dogs being diagnosed with CRGV was 3.36 times that of entire dogs (95 % CI 1.93 – 5.85; p < 0.001) (Table 2).

Discussion

This study is the first to investigate signalment risk factors for CRGV in UK dogs. Breed (p < 0.001), KC breed-group (p < 0.001), neuter status (p = 0.001) and sex (p = 0.011) were shown to be significantly associated with confirmed diagnosis of the disease. Age-group was not a significant risk factor. Two KC breed-groups – gundogs and hounds were between 9 and 10 times more likely to be diagnosed with CRGV than terriers, while no toy dogs were diagnosed with the disease. Specific breeds showing increased odds of CRGV compared with crossbreds included Hungarian Vizslas, Flat-Coated Retrievers, Whippets and English Springer Spaniels. Breeds with decreased odds included German Shepherd Dogs, Jack Russell Terriers and Staffordshire Bull Terriers. Females and neutered dogs were also more likely to be diagnosed with CRGV.

Previous studies have suggested CRGV to be associated primarily with greyhounds (Carpenter and others 1988; Cowan and others 1997; Hendricks 2000; Hertzke and others 1995) with a single instance reported of a Great Dane in Germany (Rotermund and others 2002). While Greyhounds did not have a significantly higher odds of CRGV diagnosis in this study (OR 1.65, p = 0.629) the disease (as it is currently occurring in the UK) was instead associated with multiple breeds. Compared with crossbreds, specific breeds with increased odds of being a CRGV case included the Flat-Coated Retriever (OR 84.48), Hungarian Vizsla (OR 40.98), Manchester Terrier (OR 41.41), Saluki (OR 27.46), Whippet (OR 22.43), English Springer Spaniel (OR 11.41) and Bearded Collie (OR 10.85) (Table 2). Breeds with decreased odds of being a CRGV case, when compared with crossbreds, were the Staffordshire Bull Terrier (OR 0.50), German Shepherd Dog (OR 0.45) and Jack Russell Terrier (OR 0.37). The UK KC classifies Spaniels and Retrievers as gundogs and Salukis, Whippets and Hungarian Vizslas as hounds which explains why these breed-groups were much more likely to be diagnosed with CRGV than terriers. It is possible that these breed associations result from an inherent susceptibility among these breeds as a result of genetic or behavioural patterns but it is also possible that the predisposition results from geographic confounding whereby these breeds may occur more commonly in areas with a high risk of CRGV occurrence. While CRGV has been reported from multiple locations across the UK, breed popularity varies throughout the country. A recent study by the UK KC, which analysed the breakdown of dog registrations by breed in 10 UK regions in 2016, suggested that different regions each have their own favourite top-ten breeds (http://www.telegraph.co.uk/pets/essentials/top-dog-breeds-across-the-uk/). In fact, English springer spaniels (second most likely breed diagnosed with CRGV) were among the top-ten favourite breeds in both South-East and North-West England - the two regions containing a high percentage of cases.

Breed preferences can be driven by multiple factors including body-size: large dogs are more common in rural areas while smaller dogs are generally preferred in urban areas (http://www.telegraph.co.uk/pets/essentials/top-dog-breeds-across-the-uk/). Similarly, it is logical that gundogs and hounds may predominate in rural areas where owners may participate in countryside sports such as shooting and hunting. Further studies investigating the geographic distribution of breeds and breed-groups in the UK would help to decompose the breed associations identified in this study and explore whether these breeds or breed-groups are inherently more susceptible to developing CRGV or whether areas with a higher risk of CRGV occurrence coincide with higher proportions of these breeds.

The potential reasons for associations between CRGV and being female or neutered are less clear. It has previously been reported that being female is a risk factor for certain TMAs in humans including thrombotic thrombocytopenic purpura (TTP) (Reese and others 2013), although for other TMA conditions this is not necessarily the case. There is no evidence that females in the CRGV cohort were pregnant or post-partum and indeed, although there was an association with female dogs there was also an association with neuter status.

Limitations

The denominator used in this study represented a totally primary-care population whereas the cases included some referral cases (30 %) and therefore some referral bias may have been created during selection (Bartlett and others 2010). In addition, the denominator population represented the spread of dogs under primary veterinary care during 2013 whereas the cases were recorded from 2012-2017. Breed popularity can wax and wane quite rapidly so the 2013 denominator may not exactly represent the breed spreads for each year from 2010-2017. In addition, this study classified Jack Russell Terriers as ‘not-KC recognised’ but since 2016 the KC has officially recognised this breed as belonging to the breed-group ‘terriers’. As this study identified the breed to have a decreased odds of diagnosis (OR 0.37), future studies may find the terrier breed-group to have an even lower risk of being diagnosed with CRGV than the current study depending on how Jack Russell Terriers are classified (based on period of interest and denominator population). Confidence intervals for the variables common breed and KC breed-group were comparatively wide, most likely due to the small number of CRGV cases, and suggests that these results are less robust than those variables with narrower confidence intervals. However, confidence intervals for breeds with a decreased odds of being diagnosed with CRGV were considerably narrower and more robust suggesting that greater confidence can be placed in the identification of breeds with a lower risk of being a CRGV case than those with an increased risk. A larger sample of CRGV dogs would allow for a more robust analysis.

CRGV was initially reported largely in the New Forest area of England resulting in an increased interest and awareness of the disease in this area. If certain breeds are more popular in that area then the results of this study may be biased towards those breeds. However, since seasonal outbreaks began in 2012 CRGV has been reported in other parts of the UK, and the disease has been widely publicised in national and local media, so that increased awareness is likely no longer confined to the New Forest area and therefore any potential bias arising from the New Forest focus is likely to have been mitigated over time.

Conclusion

In conclusion, the results of this study suggest that gundogs and hounds, have an increased risk of developing CRGV in the UK, while toy dogs and terriers appear to be the breed-groups least at risk. Specific breeds with increased odds of CRGV included Hungarian Vizslas, Flat-Coated Retrievers, Whippets and English Springer Spaniels. As well as helping veterinarians develop an index of suspicion for the disease, an understating of the breeds at risk may help to develop causal models for CRGV, and potentially play a role in identifying the aetiology of the disease. However, further studies investigating the distribution of specific breeds and breed-groups in the UK, and the factors driving these distributions, would help to determine whether the high-risk breeds and breed-groups identified in this study are indeed inherently more disposed to being diagnosed with CRGV or whether the results result from an increased proportion of those breeds in areas of greater risk.

Acknowledgements

This research was generously funded by the Alabama Rot Research Fund (ARRF) and New Forest Dog Owners Group (NFDog). We acknowledge the Medivet Veterinary Partnership, Vets4Pets/Companion Care, Blythwood Vets, Vets Now and the other UK practices who collaborate in VetCompass™.

Conflict of interest

The authors are not aware of any conflicts of interest.

Ethics approval

Ethics approval was granted by the RVC Ethics and Welfare Committee (reference number URN 2015 1369).

Author contributions

KS performed all analyses and wrote the first draft of the paper; LH & DW compiled the case dataset; DON compiled the VETCOMPASS™ dog denominator dataset; all authors contributed substantially to the interpretation of data, drafting of the final manuscript, and critical revision for important intellectual content. All authors approved the final version of the manuscript for submission.

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Table 1: Descriptive statistics and univariable logistic regression models showing associations between signalment variables and diagnosis with cutaneous and renal glomerular vasculopathy (CRGV) in dogs in the United Kingdom (n = 446 554)

Variable	Study population (% (n))	CRGV dogs (n=101) (% (n))	Denominator dogs (n = 446 453) (% (n))	OR (95% CI)	P-value	Wald P-value
Age-group (years)						0.038
< 1.72	24.9 (111 118)	15.8 (16)	24.9 (111 102)	Reference		
1.73 – 4.11	25.0 (111 795)	34.7 (35)	25.0 (111 760)	2.18 (1.20 – 3.92)	**0.010**	
4.12 – 7.61	25.0 (111 839)	28.7 (29)	25.0 (111 810)	1.80 (0.98 – 3.32)	0.059	
> 7.61	25.0 (111 802)	20.8 (21)	25.0 (111 781)	1.31 (0.68 – 2.50)	0.423	
Sex						**0.010**
Female	48.2 (215 104)	58.4 (59)	48.2 (215 045)	1.51 (1.02-2.25)		
Male	51.8 (231 450)	41.6 (42)	51.8 (231 408)	Reference	**0.041**	
Neuter status						**< 0.001**
Entire	38.4 (171 493)	15.8 (16)	38.4 (171 477)	Reference		
Neutered	45.5 (203 313)	69.3 (70)	45.5 (203 243)	3.69 (2.14 – 6.35)	**< 0.001**	
Not recorded	16.1 (71 748)	14.9 (15)	16.1 (71 733)	2.24 (1.11 – 4.53)	**0.025**	
Breed (pure vs cross vs designer)						0.587
Crossbred	21.8 (97 145)	18.8 (19)	21.8 (97 126)	Reference		
Purebred	75.2 (335 807)	79.2 (80)	75.2 (335 727)	1.22 (0.74 – 2.01)	0.440	
Designer	3.0 (13 602)	2.0 (2)	3.0 (13 600)	0.75 (0.18 – 3.23)	0.701	
UK Kennel Club breed-group						**<0.001**
Gundog	16.1 (72 105)	48.5 (49)	16.1 (72 056)	9.92 (3.58 – 27.49)	**< 0.001**	
Terrier	13.1 (58 362)	4.0 (4)	13.1 (58 358)	Reference		
Toy	12.6 (56 431)	0 (0)	12.6 (56 431)	Omitted	-	
Utility	9.9 (44 397)	4.0 (4)	9.9 (44 393)	1.32 (0.33 – 5.26)	0.699	
Pastoral	6.6 (29 317)	6.9 (7)	6.6 (29 310)	3.48 (1.02 – 11.90)	**0.046**	
Working	4.9 (22 001)	2.0 (2)	4.9 (21 999)	1.33 (0.24 – 7.24)	0.744	
Hound	3.5 (15 646)	11.9 (12)	3.5 (15 634)	11.20 (3.61 – 34.73)	**< 0.001**	
Not KC-recognised	33.2 (148 295)	22.8 (23)	33.2 (148 272)	2.26 (0.78 – 6.54)	0.132	
Common breed (only included if present among cases n = 258 021)						**< 0.001**
Crossbred	37.7 (97 146)	19.8 (20)	37.7 (97 126)	Reference		
Labrador Retriever	12.8 (32 938)	14.9 (15)	12.8 (32 923)	2.21 (1.13 – 4.32)	**0.020**	
Staffordshire Bull Terrier	12.5 (32 134)	3.0 (3)	12.5 (32 131)	0.45 (0.13 – 0.53)	0.201	
Jack Russell Terrier	10.6 (27 356)	2.0 (2)	10.6 (27 354)	0.36 (0.08 – 1.52)	0.163	

Cocker Spaniel	6.1 (15 671)	8.9 (9)	6.1 (15 662)	2.79 (1.27 – 6.13)	**0.011**
German Shepherd Dog	4.8 (12 321)	1.0 (1)	4.8 (12 320)	0.39 (0.05 – 2.94)	0.364
Border Collie	4.7 (12 165)	5.0 (5)	4.7 (12 160)	2.0 (0.75 – 5.32)	0.167
English Springer Spaniel	2.1 (5348)	10.9 (11)	2.1 (5337)	10.01 (4.79 – 20.90)	**< 0.001**
Beagle	1.3 (3476)	1.0 (1)	1.3 (3475)	1.40 (0.19 – 10.42)	0.744
British Bulldog	1.3 (3277)	1.0 (1)	1.3 (3276)	1.48 (0.20 – 11.05)	0.701
Greyhound	1.2 (2983)	1.0 (1)	1.2 (2982)	1.62 (0.22 – 12.14)	0.634
Lurcher	1.2 (3133)	1.0 (1)	1.2 (3132)	1.55 (0.21 – 11.56)	0.669
Whippet	0.8 (2135)	8.9 (9)	0.8 (2126)	20.56 (9.35 – 45.20)	**< 0.001**
Dalmatian	0.7 (1736)	2.0 (2)	0.7 (1734)	5.60 (1.31 – 23.98)	**0.020**
Doberman Pinscher	0.6 (1568)	2.0 (2)	0.6 (1566)	6.20 (1.45 – 26.56)	**0.014**
Weimaraner	0.6 (1539)	1.0 (1)	0.6 (1538)	3.16 (0.42 – 23.54)	0.262
Tibetan Terrier	0.4 (1003)	1.0 (1)	0.4 (1002)	4.85 (0.65 – 36.15)	0.124
Hungarian Vizsla	0.3 (775)	5.9 (6)	0.3 (769)	37.89 (15.17 – 94.61)	**< 0.001**
Flat-Coated Retriever	0.2 (452)	6.9 (7)	0.2 (445)	76.39 (32.14 – 181.57)	**<0.001**
Bearded Collie	0.2 (538)	1.0 (1)	0.2 (537)	9.04 (1.21 – 67.50)	**0.032**
Saluki	0.1 (201)	1.0 (1)	0.1 (200)	24.28 (3.23 – 181.79)	**0.002**
Manchester Terrier	0.05 (126)	1.0 (1)	0.05 (125)	38.85 (5.17 – 291.70)	**< 0.001**

Table 2: Multivariable logistic regression results for variables significantly associated with diagnosis with cutaneous and renal glomerular vasculopathy (CRGV) in dogs in the United Kingdom. The variable breed was included as common breed (Model 1) and as the derived variable Kennel Club breed-group (Model 2)

Model 1 (Breed included as common breed)			Model 2 (Breed included as KC breed-group)		
Variable	**OR (95% CI)**	**P-value**	**Variable**	**OR (95% CI)**	**P-value**
Sex			**Sex**		
Female	1.49 (1.00 – 2.21)	**0.049**	Female	1.51 (1.02 – 2.24)	**0.042**
Male	Reference		Male	Reference	
Neuter status			**Neuter status**		
Entire	Reference		Entire	Reference	
Neutered	3.35 (1. 92 – 5.85)	**< 0.001**	Neutered	3.36 (1.93 – 5.85)	**< 0.001**
Not recorded	1.62 (0.79 – 3.32)	0.187	Not recorded	1.95 (0.96 – 3.98)	**0.065**
Breed (included in model as common breed)			**Breed (included in model as common KC breed-group)**		
Crossbred	**Reference**		Not KC-recognised	2.12 (0.73 – 6.12)	0.167
Lurcher	1.63 (0.22 – 12.15)	0.634			
Jack Russell Terrier	0.37 (0.09 – 1.58)	0.179			
Manchester Terrier	41.41 (5.49 – 312.22)	**< 0.001**	Terrier	**Reference**	
Staffordshire Bull Terrier	0.50 (0.15 – 1.70)	0.268			
Saluki	27.46 (3.65 – 206.32)	**0.001**	Hound	10.68 (3.44 – 33.13)	**< 0.001**
Whippet	22.43 (10.18 – 49.42)	**< 0.001**			
Greyhound	1.64 (0.22 – 12.30)	0.629			
Beagle	1.33 (0.18 – 9.94)	0.780			
Flat-Coated Retriever	84.48 (35.19 – 202.80)	**<0.001**	Gundog	9.69 (3.50 – 28.86)	**< 0.001**
Hungarian Vizsla	40.98 (16.34 – 102.75)	**<0.001**			
English Springer Spaniel	11.41 (5.44 – 23.94)	**< 0.001**			
Weimaraner	3.20 (0.43 – 23.90)	0.257			
Cocker Spaniel	2.91 (1.32 – 6.39)	**0.008**			
Labrador Retriever	2.35 (1.20 – 4.61)	**0.012**			
Bearded Collie	10.85 (1.45 – 81.34)	**0.020**	Pastoral	3.50 (1.01 – 11.96)	**0.046**
Border Collie	2.06 (0.77 – 5.50)	0.148			
German Shepherd Dog	0.45 (0.06 – 3.38)	0.440			
Doberman Pinscher	6.87 (1.60 – 29.47)	**0.009**	Working	1.37 (0.25 – 7.49)	0.716
Dalmatian	5.79 (1.35 – 24.80)	**0.018**	Utility	1.32 (0.33 – 5.28)	0.695
Tibetan Terrier	5.24 (0.70 – 39.12)	0.107			
British Bulldog	1.94 (0.23– 14.55)	0.518			