Chronic kidney disease in dogs in UK veterinary practices: prevalence, risk factors and survival

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Canine chronic kidney disease

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Abbreviations:

CI, Confidence Interval; CKCS, Cavalier King Charles Spaniels; CKD, Chronic Kidney Disease; EPR, Electronic Patient Records; IRIS, International Renal Interest Society; KC , Kennel Club; OR, Odds Ratio; RSPCA, Royal Society for the Prevention of Cruelty to Animals; SQL , Structured Query Language; UK, United Kingdom; US, United States

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Abstract

Background- The prevalence for chronic kidney disease (CKD) in dogs varies widely (0.05% - 3.74%). Identified risk factors include advancing age, specific breeds, small body-size and periodontal disease.

Hypothesis/Objectives- To estimate the prevalence and identify risk factors associated with CKD diagnosis and survival in dogs. Purebred dogs were hypothesised to have higher CKD risk and poorer survival characteristics than crossbred dogs.

Animals- A merged clinical database of 107,214 dogs attending 89 UK veterinary practices over a 2-year period (January 2010-December 2011).

Methods- A longitudinal study design estimated the apparent prevalence (AP) while the true prevalence (TP) was estimated using Bayesian analysis. A nested case-control study design evaluated risk factors. Survival analysis used the Kaplan-Meier survival curve method and multivariable Cox proportional hazards regression modeling.

Results- The CKD AP was 0.21% (95% CI: 0.19-0.24%) and TP was 0.37% (95% posterior credibility interval 0.02-1.44%). Significant risk factors included increasing age, being insured and certain breeds (Cocker Spaniel, Cavalier King Charles Spaniel). Cardiac disease was a significant co-morbid disorder. Significant clinical signs included halitosis, weight loss, polyuria/polydipsia, urinary incontinence, vomiting, decreased appetite, lethargy and diarrhea. The median survival time from diagnosis was 226 days (95% CI 112-326 days). IRIS stage and blood urea nitrogen concentration at diagnosis were significantly associated with hazard of death due to CKD.

Conclusions and clinical importance- CKD compromises dog welfare. Increased awareness of CKD risk factors and association of blood biochemistry results with survival-time should facilitate diagnosis and optimize case management to improve animal survival and welfare.

Introduction

Chronic kidney disease (CKD) is defined as the presence of structural or functional abnormalities of one or both kidneys that have been present for an extended period, usually 3 months or longer [1]. Despite being initiated by a heterogeneous variety of familial, congenital and acquired factors, the end result of canine CKD is a reduced total kidney glomerular filtration rate and the consequences of this to homeostasis [2]. CKD is said to be the most common kidney disease in dogs [3] but estimates of prevalence vary widely depending on the source population and the case inclusion criteria from 0.05% [4], 0.9% [3], 0.5-1.5% [5] to 3.74% [6].

Studies reporting *apparent* prevalence values reflect the prevalence of clinical diagnoses but fail to account for the often unknown effects of false positive and false negative results. Bayesian statistical techniques incorporate such uncertainty and variability by analyzing estimated sensitivity and specificity distributions for clinical diagnosis to derive true prevalence values with appropriate confidence intervals [7].

Although CKD is ultimately a progressive disorder, early diagnosis and management may modify the rate of progression and improve patient quality and quantity of life [8-11]. Demographic

risk factors previously identified for CKD include advancing age[4,6,12,13] , small size [14] and specific breeds with familial kidney disease including the Chinese Shar Pei[15], Bull Terrier [16], English Cocker Spaniel [17], West Highland White Terrier [18] and Boxer [19]. Periodontal disease has been identified as a clinical risk factor for CKD [14,20].

The International Renal Interest Society (IRIS) has proposed a progressing 4-stage scoring system for canine CKD based on blood biochemical testing, urinalysis results and systemic arterial blood pressure [21] that categorizes CKD cases to facilitate diagnosis, treatment, prognosis and research [22]. Clinically affected dogs present at various points along the IRIS stages [1] but the majority of CKD cases ultimately converge to the uraemic state, characterized by multiple severe physiologic and metabolic derangements of impaired kidney function [3]. Dogs in IRIS stages 3 and 4 survive from a few months to 2 years with most dying or being euthanized because of their disease [1].

The primary objectives of this study were to estimate the prevalence of CKD among dogs attending UK primary care veterinary practices, to identify demographic and clinical risk factors associated with CKD diagnosis and survival and to describe survival characteristics following diagnosis. Purebred dogs were hypothesised to experience higher CKD risk and poorer survival characteristics than crossbred dogs.

Materials and Methods

A longitudinal study design followed dogs attending participating practices over time and estimated the prevalence of CKD diagnosis in dogs from all electronic patient records (EPRs)

between 1st January 2010 and 31st December 2011 within the VetCompass Animal Surveillance project [23]. Practices were selected by willingness to participate and were mainly in central and south-eastern England. A nested case-control study design evaluated risk factors associated with CKD diagnosis and survival. Control animals were selected using a web-based random number generator [24] with exclusion of animals having a history indicative of kidney disease. Sample size calculations [25] estimated an unmatched case-control study with 209 cases and 209 controls would have an 80% power to detect a risk factor with an odds ratio of 2.0 or greater (two-sided α=0.05) having a 15% prevalence in the control animals.

Summary diagnosis terms from the VeNom Code list of veterinary-specific terms were recorded at episodes of clinical care [26]. EPRs were extracted using an integrated clinical query [27] and uploaded to a secure structured query language (SQL) database. Clinical fields shared included unique clinic and animal identification numbers, birth-date, species, breed, sex, neuter status, insured status, consultation date, bodyweight, clinical notes, summary diagnosis term and treatment details. Ethics approval was granted by the Royal Veterinary College Ethics & Welfare Committee (reference number 2010 1076).

Dog breeds were sub-categorized for analysis using three systems: purebred/crossbred; breed Kennel Club (KC) status (registered/not registered) and breed KC group status (gundog, hound, pastoral, terrier, toy, utility, working) [28]. Breeds with 12 or more dogs within the case:control part of the study were evaluated separately (Table 1). The final recorded weight, insurance and neuter status was included for analysis. The age at the final live record was included for the case-control study while the age at diagnosis was used for survival analysis. Age (years) was

categorized into 4 rounded quantiles; <4, 4-7, 7-12 and >12 while weight (kg) was categorized into 5 rounded quantiles: <7, 7-11, 11-20, 20-30, and >30. Clinical laboratory results were available only when transcribed by practitioners to the clinical notes. Cases with available blood creatinine concentration (mg/dl) at diagnosis were staged using IRIS guidelines; Stage 1: <1.4, Stage 2: 1.4-2.0, Stage 3: 2.1-5.0, Stage 4: >5.0 with Stage 1 and 2 collapsed for analysis [21]. Dogs with blood urea nitrogen concentration (mg/dl) available at diagnosis were categorized into 4 groups: <44.8, 44.8 to <64.4, 64.4 to <112.0 and ≥112.0.

Preliminary CKD case identification used VeNom diagnosis terms (chronic kidney (renal) disease, renal (kidney) disorder) and free-text searching of clinical notes (renal, kidney, CKD, CRD, CKF, CRF, azot*, urem*, uraem*). The CKD case definition relied on primary practitioner diagnosis based on clinical acumen and synthesis of their medical knowledge of the animal including anamnesis, physical examination and laboratory testing that was not necessarily formally recorded within the clinical notes. Specifically, case inclusion criteria required both i) a summary diagnosis term, insurance claim term or free-text diagnosis of CKD with a consistent history and ii) evidence that blood biochemistry analysis assisted the diagnosis process. CKD diagnosis date was defined as the first drawing of a confirmatory blood sample. Where diagnosis preceded available records, prior clinical histories (n=15) were sourced. Clinical laboratory values (creatinine, urea, phosphate) at diagnosis and urinalysis results obtained closest to the diagnosis date (maximum 28-day window) were recorded. Dates for the earliest and latest live animal EPR, all documented clinical signs and co-morbid disorders and, for animals dying during the study, the cause of death (if natural) or stated reason for euthanasia were recorded.

Following spreadsheet checking and cleaning (Microsoft Office Excel 2007, Microsoft Corp.), all analysis used Stata Version 11.2 (Stata Corporation) except for true prevalence (TP) estimation. Bayesian analysis implemented in OpenBUGS version 3.2.1 rev 781 [29,30] derived TP based on a non-informative prevalence prior, the estimated AP and expert opinion provided by one of the authors (JE) for primary practice diagnostic sensitivity (Se) (the proportion all true CKD cases that are correctly diagnosed as CKD) and diagnostic specificity (Sp) (the proportion of all true non-CKD animals that were correctly classified as non-CKD) values. Low Se (20%, with 95% confidence of being under 33%) and high Sp (99.5%, with 95% confidence of being above 98%) values were selected because of the expense and complexity of CKD diagnosis and the case definition used [31]. Beta prior distributions were parameterized using the BetaBuster program [32].

Demographic risk factors with a P-value <0.20 in univariable logistic regression and purebred status (variable of *a priori* interest) were evaluated using multivariable logistic regression. Model building used manual backwards elimination. All eliminated factors were re-evaluated for confounding effects within the provisional-final model before confirming their removal. Biologically meaningful pairwise interactions were assessed between the final model variables. An effect of clustering at the clinic level was evaluated in the final model using the clinic attended as a random effect [33]. Model fit diagnostics were evaluated (Hosmer and Lemeshow 2000). Statistical significance was set at P=0.05. The univariable association between CKD and purebred/crossbred status for dogs less than 5 years old was additionally evaluated using Fisher's exact test [34].

Co-morbid disorders and clinical signs univariably associated with CKD (P<0.20) were evaluated for adjusted association (P<0.05) by individual addition to the final demographic multivariable regression model. For complete separation (zero-cells), the Stata *firthlogit* program allowed inference based on the profile penalized likelihood [35].

Median survival time from diagnosis was estimated using the Kaplan-Meier method with differences between categories evaluated by the log-rank test. Explanatory variables with P<0.20 in univariable Cox proportional hazards regression models and purebred status were assessed using multivariable Cox modelling. Model fitting used a manual backwards elimination approach with significance set at P<0.05. The proportionality assumption was tested using Schoenfeld and scaled Schoenfeld residuals and the fit of the final model to the data was checked using Cox-Snell residuals.

Results

Overall, 228 dogs met the CKD inclusion criteria from 107,214 dogs attending 89 practices. The CKD AP was 0.21% (95% CI: 0.19-0.24%). Using Bayesian inference, the CKD TP was estimated to be 0.37% (95% posterior credibility interval 0.02-1.44%).

Of the case dogs, 190/228 (83.3%) were purebred, 115/228 (50.4%) were female, 173/228 (75.9%) were neutered, 126/227 (55.5%) were insured and 145/228 (63.6%) were aged over 12 years at diagnosis. The most frequently affected breeds were the Yorkshire Terrier, Jack Russell Terrier and West Highland White Terrier (Table 1). At diagnosis, 95/136 dogs (69.9%) were

IRIS Stage 3 or 4 while 37/139 (26.6%) had blood urea nitrogen concentrations at or above 112.0 mg/dl/l. During the study period, 118/228 (51.8%) dogs died of CKD with 99/118 (83.9%) of these being euthanized.

Risk factor analysis

The variables taken forward from univariable analysis but not retained following multivariable modeling included purebred status (*a priori* interest), neuter status and bodyweight category (Table 1). Demographic risk factors significantly associated with a diagnosis of CKD included age group, insured status and breed (Table 2). The results of multivariable analysis indicated that dogs aged 12 years and above had 5.49 (95%CI: 2.84-10.60, P<0.001) times the odds and dogs aged between 4 and 7 years had 0.22 (95%CI: 0.10-0.48, P<0.001) times the odds of CKD compared with dogs aged between 7 and 12 years. Insured animals had 2.55 (95%CI: 1.50-4.33, P<0.001) times the odds of CKD of uninsured dogs. Cocker Spaniels (odds ratio (OR) 6.39, 95%CI: 1.63-25.00, P=0.008) and Cavalier King Charles Spaniels (CKCS) (OR 5.57, 95%CI: 1.07-28.97, P=0.041) had increased odds of CKD compared with crossbreds. Clustering within the veterinary clinic attended did not improve the model (P = 0.4273). No significant interactions were found. The Hosmer-Lemeshow test indicated good model fit (P=0.7285). The area under ROC curve was 0.8783, indicating excellent CKD discrimination [36].

For dogs aged less than 5 years, purebred/crossbred status was not associated with CKD (P=0.218).

Co-morbid disorders and clinical signs

The most frequent CKD co-morbid disorders recorded were gingivitis/periodontitis (69 cases, 30.3%), cardiac disorders (68, 29.8%) and musculoskeletal disorders (56, 24.6%). Following adjustment, disorders significantly associated with CKD included hypertension (OR: 25.71, 95% CI 1.38-479.20, P<0.001) and cardiac disease (OR: 3.88, 95%CI 1.69-8.90, P<0.001) (Table 3).The most frequent clinical signs of CKD cases were vomiting (114 dogs, 50.0%), polyuria/polydipsia (100, 43.9%) and appetite decreased/anorexia (90, 39.5%). Significantly associated clinical signs included halitosis (OR: 57.03, 95%CI 3.16-1030.50, P<0.001), anaemia (OR: 40.71, 95%CI 2.00-827.66, P<0.001), weight loss/cachexia (OR: 12.89, 95%CI 4.81-34.55, P<0.001), polyuria/polydipsia (OR: 7.70, 95%CI 3.53-16.82, P<0.001), urinary incontinence (OR: 4.97, 95%CI 1.72-14.37, P<0.001) and vomiting (OR: 4.57, 95%CI 2.53-8.24, P<0.001) (

Table **3**).

Survival analysis

Using a Kaplan-Meier survival curve, the median survival time from CKD diagnosis until death due to CKD (including euthanasia) was 226 days (95% CI 112-326 days). No demographic variables were significantly associated with survival differences but IRIS stage (P<0.001) (Figure 1) and blood urea nitrogen concentration (P<0.001) (Figure 2) were significantly associated.

No demographic variables were significant in univariable Cox regression analysis. Blood phosphate concentration, urine specific gravity at diagnosis and purebred status were taken forward to Cox multivariable modeling but not retained. The final Cox regression model included IRIS stage and urea nitrogen concentration (Table 4). Compared with IRIS Stage 1 and 2 combined, dogs in IRIS Stage 3 at diagnosis showed 2.62 (95% CI 1.14-6.01, P=0.023) times and dogs in IRIS Stage 4 had 4.71 (95%CI 1.74-12.72, P=0.002) times the hazard of death from CKD. Dogs with blood urea nitrogen concentrations of 112.0 mg/dl or greater at diagnosis had 7.76 (95% CI 2.65-22.74, P<0.001) times the hazard of death from CKD compared with those with blood urea nitrogen concentrations below 44.8 mg/dl. There was no evidence of interaction in the final model. The model assumptions were met and the model fitted the data adequately.

Discussion

This large study of dogs attending UK practices showed a relatively low but clinically relevant CKD prevalence (AP 0.21%, Bayesian TP 0.37%) and identified increased diagnosis among

older and insured dogs as well as certain breeds. Cardiac disease was significantly associated with CKD. Additional consideration of halitosis and urinary incontinence as diagnostically-predictive clinical signs should improve diagnostic sensitivity. IRIS staging and blood urea nitrogen concentrations at diagnosis enhanced prognostic prediction. Purebred dogs did not show higher CKD risk or poorer survival than crossbreds, either overall or within dogs aged below 5 years.

The CKD prevalence indicated by this study is at the lower end of the reported 0.05-3.74% spectrum from previous studies [3-6] which were based on varying denominator population calculations and CKD definitions. Prevalence estimates derived from referral caseloads are likely to poorly represent the overall population and to over-represent CKD prevalence [37]. CKD case definitions in earlier studies ranged from just a single blood biochemical analysis and urinalysis [4] to repeated blood biochemistry analysis with renal histopathology and ultrasonography [6]. The current analysis used the entire known study population as the denominator and the case definition reflected primary practice diagnostic norms to ensure relevance for primary practitioners.

Most prevalence studies report apparent prevalence (prevalence of diagnoses made) rather than true prevalence (prevalence of all true cases) because of imperfect clinical tests [38]. Within a clinical environment, all animal evaluations (including clinical examinations and laboratory tests) can be considered diagnostic tests and combinations of these tests could be considered as an overall CKD diagnosis test. The consequences of test errors include false negative (true cases that are missed) and false positives (non-cases that are diagnosed as cases). Although rare, where

diagnostic sensitivity and specificity are known, true prevalence can be calculated by formulaic adjustment within the frequentist statistical paradigm [33]. Bayesian analytic methods are increasingly applied to veterinary epidemiologic data to formally incorporate prior information and expert opinion into prevalence calculations [31] and to estimate the true prevalence of disease. The current study results estimated CKD true prevalence (TP) (0.37%) to be almost twice as high as the apparent prevalence (AP) (0.21%), suggesting failure to reach a final diagnosis in a substantial proportion of cases. It should be noted that the Bayesian estimates included expert opinion for Se and Sp values. An inconsistent opinion would have yielded differing results.

Elucidation of demographic and clinical CKD risk factors could improve diagnostic sensitivity and timeliness [39] and optimize primary-cause and conservative case management with consequent animal welfare gains[9]. Demographic CKD risk factors identified in this study included advancing age, being insured and specific breeds. Dogs older than 12 years had over 5 times the odds of CKD compared with dogs aged 7-12 years, concurring with several previous reports [3,5,40] and supporting the theory of CKD progression from early subclinical kidney damage to clinical disease [40].

Non-insured animals were less than half as likely to receive a CKD diagnosis as insured animals, agreeing with Swedish pet insurance analysis where non-insured animals were believed to access veterinary care less often and undergo fewer medical procedures such as blood tests compared with insured animals [41]. Given that the recommended minimum CKD clinical database includes a range of hematology, blood biochemistry and urinalysis tests [42], these results suggest financial

constraints to diagnosis are compromising dog welfare and partially explain imperfect diagnostic sensitivity.

Familial renal disease generally results in CKD before 5 years of age [43]. Purebred dogs did not show increased CKD odds, either overall or for dogs aged below 5 years, or increased hazard compared with crossbred dogs. Hybrid dogs are stated to generally grow bigger and stronger than their purebred parents [44] and it was hypothesised that crossbred health would benefit from this hybrid vigor effect [45] combined with reduced familial effects. Many UK crossbred dogs are purebred hybrids with recognizable phenotypes from one or more genealogical breeds and may retain inbreeding depression effects of the parental breeds [46]. Specific canine hybrid breeding programs are growing in popularity but further studies on diverse disorders and with larger case numbers are needed to establish the true extent of any suggested hybrid health benefits [47]. Other reported breed-related causes of CKD (e.g. cardiovascular [48], immunologic [4], neoplasia [49], renal calculi [50]) could have contributed to the Cocker Spaniel and CKCS breed predispositions identified. The CKD odds ratio increased from univariable to multivariable analysis for the Cocker Spaniel (1.73 to 6.39) and CKCS (2.72 to 5.57) because of the younger age distribution and lower insurance status for these breeds relative to many other breeds analysed (data not shown). This highlights improved interpretation resulting from multivariable analyses that account for confounding effects within epidemiological studies.

Vigilance for co-morbid disorders that worsen the CKD condition may improve the situation by appropriate management [8] as well as increasing diagnostic sensitivity. Cardiac disease remained significantly associated with CKD following adjustment for age, insurance and breed. Renal

impairment has previously been shown to increase with the severity of congestive heart failure and to be a frequent finding in dogs with chronic valvular disease [51]. The low prevalence of hypertension (6.1%) identified among CKD cases contrasts with the 50-93% level reported by Bartges et al.[52] and may reflect sub-optimal use of blood pressure monitoring among primary practice caseloads.

Although previously identified as an important predictor for canine CKD[14], the current study did not identify an association with smaller body size. Despite affecting over 30% of CKD cases, gingivitis/periodontitis was not a significant risk factor because of its widespread occurrence; 19.5% (95% CI: 20.0-20.9%) of US private practice dogs were reported to show gingivitis[53].

Distressing clinical signs are believed to indicate suffering but there is no current system to rank their welfare impact [54]. This study re-affirms several previously reported and unpleasant CKD clinical signs (weight loss, polyuria/polydipsia, anaemia, urinary incontinence, vomiting and diarrhea[2,3,14]) establishing CKD as a disorder that can compromise dog welfare appreciably. Counseling owners on the clinical relevance of these signs, especially halitosis[14], should encourage earlier presentation and diagnosis[55] with consequent enhancements to life quality and quantity[8].

Increasing IRIS stage and blood urea nitrogen concentration at diagnosis were both associated with decreased survival time. Formal IRIS staging recommendations include assessment of fasting plasma creatinine concentrations on at least two occasions in the stable patient, with sub-staging based on proteinuria and systemic blood pressure. The current study adapted these guidelines by staging from a single creatinine measurement at diagnosis to reduce selection bias

and reflect primary practice diagnostic protocols. The survival effects associated with IRIS stages supports their in-practice use for CKD case management and prognosis [21].

There were some limitations to the current study. Although practice selection was a convenience sample mainly in central and south-east England, the high number of participating practices (89) should assure generalisability. Clinical laboratory results were available only when transcribed to the clinical notes, introducing possible transcription error and bias. The inclusion of co-morbid disorder diagnoses relied upon the attending veterinarian detecting and recording the concurrent disease. The performance and results of positive tests (e.g. a dog has hypertension) may be more likely to be recorded than information related to tests that are found to be negative (e.g. a dog does not have hypertension). Case notes without a recorded co-morbid disorder did not necessarily imply that the animal was either evaluated or tested negative for this disorder.

CKD in dogs is an important welfare disorder because of its clinically relevant prevalence, unpleasant clinical signs and impact on case survival. Increased awareness of the demographic and clinical risk factors identified in this study should lead to earlier and improved diagnosis with optimized case management for improved survival and animal welfare. The interpretation of blood biochemistry results should improve the accuracy of prognostic estimation for individual cases.

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Table 1. Descriptive and univariable logistic regression results for risk markers associated with canine chronic kidney disease

Variable		Case no. (%)	Control no. (%)	Odds ratio	95% CI	P-Value
Purebred						
	No	38 (16.7)	46 (20.2)	Referent	Referent	Referent
	Yes	190 (83.3)	182 (79.8)	1.26	0.79-2.03	0.334
Kennel Club registered breed						
	No	57 (25.0)	66 (28.9)	Referent	Referent	Referent
	Yes	171 (75.0)	162 (71.1)	1.22	0.81-1.85	0.343
Breeds (named if ≥ 12 study dogs)						
	Crossbred	38 (16.7)	46 (20.2)	Referent	Referent	Referent
	Breeds with <12 study dogs	91 (39.9)	84 (36.8)	1.31	0.78-2.21	0.309
	Border Collie	10 (4.4)	2 (0.9)	6.05	1.25-29.32	0.025
	Cavalier King Charles Spaniel	9 (3.9)	4 (1.8)	2.72	0.78-9.54	0.117
	Cocker Spaniel	10 (4.4)	7 (3.1)	1.73	0.60-4.98	0.310
	Jack Russell Terrier	18 (7.9)	17 (7.5)	1.28	0.58-2.82	0.538
	Labrador Retriever	9 (3.9)	19 (8.3)	0.57	0.23-1.41	0.227
	Shih Tzu	6 (2.6)	8 (3.5)	0.91	0.29-2.85	0.868
	Staffordshire Bull Terrier	4 (1.8)	26 (11.4)	0.19	0.06-0.58	0.004
	Yorkshire Terrier	19 (8.3)	10 (4.4)	2.30	0.96-5.53	0.063
	West Highland White Terrier	14 (6.1)	5 (2.2)	3.39	1.12-10.26	0.031
Sex						
	Female	115 (50.4)	106 (46.5)	Referent	Referent	Referent
	Male	113 (49.6)	122 (53.5)	0.85	0.59-1.23	0.399
Neuter status						
	No	55 (24.1)	114 (50.0)	Referent	Referent	Referent
	Yes	173 (75.9)	114 (50.0)	3.15	2.11-4.69	<0.001
Age category						
	Less than 4 years	9 (3.9)	114 (50.0)	0.06	0.03-0.14	<0.001

	4 to less than7 years	16 (7.0)	42 (18.4)	0.31	0.15-0.62	0.001
	7 to less than 12 years	58 (25.4)	47 (20.6)	Referent	Referent	Referent
	12 years and older	145 (63.6)	25 (11.0)	4.70	2.65-8.33	<0.001
Weight category						
	Less than 7kg	39 (17.1)	44 (19.3)	Referent	Referent	Referent
	7kg to less than 11kg	58 (25.4)	29 (12.2)	2.26	1.21-4.19	0.010
	11kg to less than 20kg	59 (25.9)	39 (17.1)	1.71	0.95-3.08	0.076
	20kg to less than 30kg	33 (14.5)	45 (19.7)	0.83	0.44-1.54	0.551
	30kg and above	26 (11.4)	41 (18.0)	0.72	0.37-1.38	0.315
Insured status						
	No	101 (44.3)	135 (59.2)	Referent	Referent	Referent
	Yes	126 (55.3)	79 (34.6)	2.13	1.46-3.12	<0.001

Table 2. Final multivariable logistic regression model for a primary practice case:control study of risk factors associated with canine chronic kidney disease (228 cases and 228 controls)

Risk Factor		Odds Ratio	95% CI	P-value
Age group (years)				
	Under 4	0.06	0.03-0.14	<0.001
	4 to <7	0.22	0.10-0.48	<0.001
	7 to <12	Referent	Referent	Referent
	Over 12	5.49	2.84-10.60	<0.001
Insured status				
	Uninsured	Referent	Referent	Referent
	Insured	2.55	1.50-4.33	<0.001
Breeds (named if ≥ 12 study dogs)				
	Crossbred	Referent	Referent	Referent
	Breeds with <12 study dogs	2.58	1.24-5.38	0.011
	Border Collie	7.65	0.83-70.51	0.073
	Cavalier King Charles Spaniel*	5.57	1.07-28.97	0.041
	Cocker Spaniel*	6.39	1.63-25.00	0.008
	Jack Russell Terrier	1.56	0.54-4.54	0.415
	Labrador Retriever	0.53	0.16-1.72	0.292
	Shih Tzu	1.45	0.26-8.07	0.674
	Staffordshire Bull Terrier	0.84	0.21-3.46	0.815
	West Highland White Terrier	1.38	0.36-5.27	0.638
	Yorkshire Terrier	1.47	0.48-4.52	0.506

*Individual breed with significantly higher CKD odds than crossbreds

Table 3. Co-morbid disorders and clinical signs having significant association (P<0.05) with canine chronic kidney disease when individually added to a multivariable logistic regression model of primary practice dogs that also included age group, insured status and common breed variables

	No. Cases (%)	No. Controls (%)	Odds Ratio	95% C.I.	P-Value
Disorder diagnosed					
Hypertension*	14 (6.1)	0 (0.0)	25.71	1.38-479.20	<0.001
Pancreatitis*	11 (4.8)	0 (0.0)	16.96	0.69-414.01	0.021
Cardiac disorder	68 (29.8)	13 (5.7)	3.88	1.69-8.90	<0.001
Clinical sign					
Halitosis*	27 (11.8)	0 (0.0)	57.03	3.16-1030.50	<0.001
Anaemia*	9 (3.9)	0 (0.0)	40.71	2.00-827.66	<0.001
Weight loss/Cachexia	66 (28.9)	6 (2.6)	12.89	4.81-34.55	<0.001
Polyuria/Polydipsia	100 (43.9)	10 (4.4)	7.70	3.53-16.82	<0.001
Urinary incontinence	45 (19.7)	5 (2.2)	4.97	1.72-14.37	<0.001
Vomiting	114 (50.0)	38 (16.7)	4.57	2.53-8.24	<0.001
Appetite decreased/ Anorexia	90 (39.5)	26 (11.4)	3.66	1.93-6.94	<0.001
Lethargy/ depressed	50 (21.9)	21 (9.2)	3.34	1.59-7.02	<0.001
Diarrhoea/Melaena	85 (37.3)	38 (16.7)	2.29	1.26-4.16	0.006

*Stata *firthlogit* modelling used because of complete separation

Figure 1. Kaplan-Meier survival curves for dogs diagnosed with CKD grouped by IRIS stage at diagnosis showing reducing survival with increasing IRIS stage.

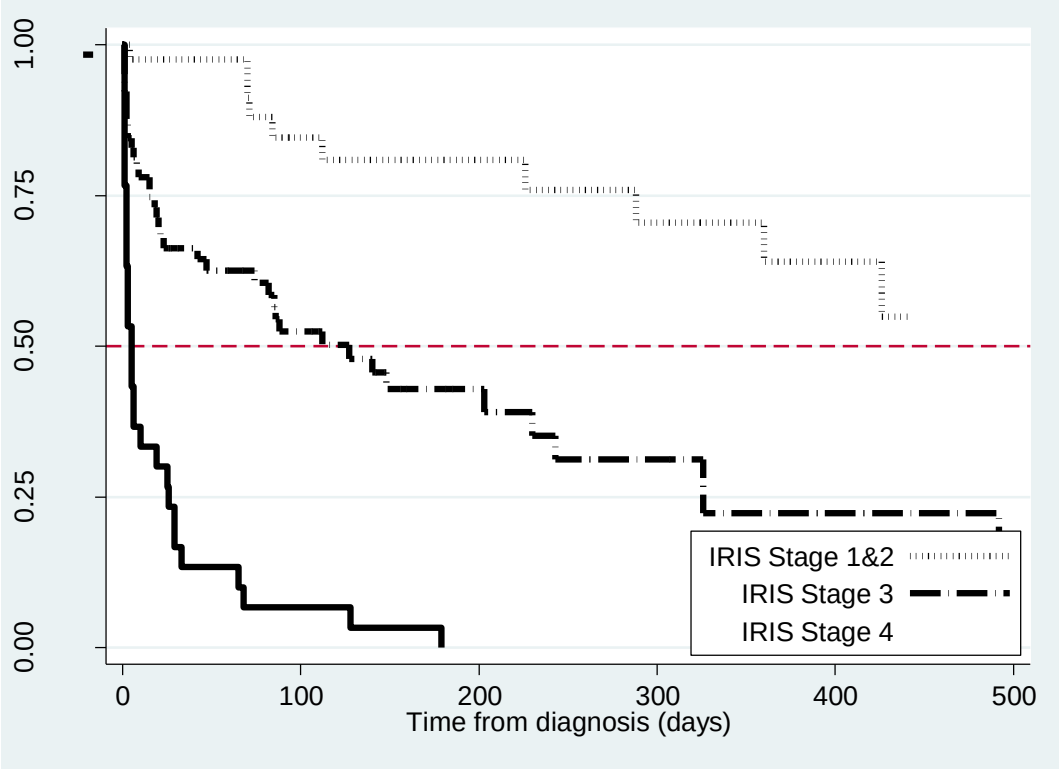

Figure 2. Kaplan-Meier survival curves for dogs diagnosed with CKD grouped by blood urea nitrogen concentration (mg/dl) at diagnosis showing reducing survival with increasing blood urea nitrogen concentration.

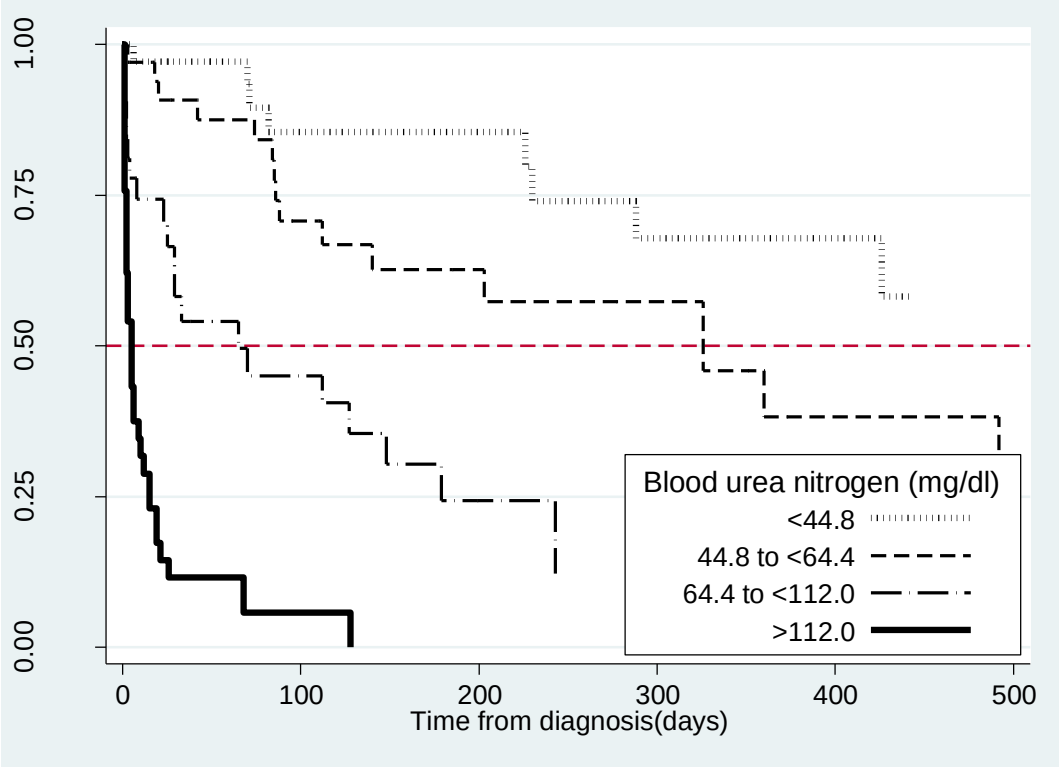

Table 4. Final multivariable Cox regression model for risk factors associated with death among primary veterinary practice dogs diagnosed with chronic kidney disease

Risk Factor		No. cases (%)	Hazard Ratio	95% CI	P-value
Iris stage at diagnosis					
	1 or 2	41 (30.1)	Referent	Referent	Referent
	3	65 (47.8)	2.62	1.14-6.01	0.023
	4	30 (22.1)	4.71	1.74-12.72	0.002
Blood Urea at diagnosis (mg/dl)					
	Less than 44.8	33 (23.7)	Referent	Referent	Referent
	44.8 to less than 64.4	37 (26.6)	1.24	0.48-3.16	0.659
	64.4 to less than 112.0	32 (23.0)	2.60	0.98-6.90	0.055
	112.0 and above	37 (26.6)	7.76	2.65-22.74	<0.001