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Canine chronic kidney disease in UK veterinary practices: prevalence, risk factors and survival

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Chronic Kidney Disease in Dogs in UK Veterinary Practices: Prevalence, Risk Factors, and Survival

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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 hypothesized 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) whereas 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 comorbid 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). International Renal Interest Society stage and blood urea nitrogen concentration at diagnosis were significantly associated with hazard of death due to CKD.

Conclusions and Clinical Importance: Chronic kidney disease 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.

Key words: Epidemiology; Primary practice; Prognostic indicator; Purebred; Renal.

Chronic kidney disease (CKD) is defined as the presence of structural or functional abnormalities of 1 or both kidneys that have been present for an extended period, usually 3 months or longer.[1] Although initiated by a heterogeneous variety of familial, congenital, and acquired factors, the end result of CKD in dogs is 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]

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

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 CKD in dogs 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

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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 after diagnosis. Purebred dogs were hypothesized 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 January 1, 2010 and December 31, 2011 within the VetCompass Animal Surveillance project.[23] Practices were selected by willingness to participate and were mainly in central and southeastern 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 $\alpha = 0.05$) 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 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).

Breeds of dogs were subcategorized for analysis using 3 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 were included for analysis. The age at the final live record was included for the case-control study whereas the age at diagnosis was used for survival analysis. Age (years) was categorized into 4 rounded quantiles; <4, 4–7, 7–12, and >12 whereas 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 $\geq$ 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 comorbid 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, Redmond, WA), all analysis used Stata Version 11.2 (Stata Corporation, TX) except for true prevalence (TP) estimation. Bayesian analysis implemented in OpenBUGS version 3.2.1 rev 781[29,30] derived TP based on a noninformative prevalence prior, the estimated apparent prevalence (AP) and expert opinion provided by one of the authors 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 <.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 reevaluated 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). Statistical significance was set at $P = .05$. 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]

Comorbid disorders and clinical signs univariably associated with CKD ($P < .20$) were evaluated for adjusted association ($P < .05$) 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 $P < .20$ in univariable Cox proportional hazards regression models and purebred status were assessed using multivariable Cox modeling. Model fitting used a manual backward elimination approach with significance set at $P < .05$. 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

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

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	.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	.343
Breeds (named if $\geq$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	.309
Border Collie	10 (4.4)	2 (0.9)	6.05	1.25–29.32	.025
Cavalier King Charles Spaniel	9 (3.9)	4 (1.8)	2.72	0.78–9.54	.117
Cocker Spaniel	10 (4.4)	7 (3.1)	1.73	0.60–4.98	.310
Jack Russell Terrier	18 (7.9)	17 (7.5)	1.28	0.58–2.82	.538
Labrador Retriever	9 (3.9)	19 (8.3)	0.57	0.23–1.41	.227
Shih Tzu	6 (2.6)	8 (3.5)	0.91	0.29–2.85	.868
Staffordshire Bull Terrier	4 (1.8)	26 (11.4)	0.19	0.06–0.58	.004
Yorkshire Terrier	19 (8.3)	10 (4.4)	2.30	0.96–5.53	.063
West Highland White Terrier	14 (6.1)	5 (2.2)	3.39	1.12–10.26	.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	.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	<.001
Age category					
Less than 4 years	9 (3.9)	114 (50.0)	0.06	0.03–0.14	<.001
4 to less than 7 years	16 (7.0)	42 (18.4)	0.31	0.15–0.62	.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	<.001
Weight category					
Less than 7 kg	39 (17.1)	44 (19.3)	Referent	Referent	Referent
7 kg to less than 11 kg	58 (25.4)	29 (12.2)	2.26	1.21–4.19	.010
11 kg to less than 20 kg	59 (25.9)	39 (17.1)	1.71	0.95–3.08	.076
20 kg to less than 30 kg	33 (14.5)	45 (19.7)	0.83	0.44–1.54	.551
30 kg and above	26 (11.4)	41 (18.0)	0.72	0.37–1.38	.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	<.001

AP was 0.21% (95% CI: 0.19–0.24%). Using Bayesian inference, the CKD TP was estimated to be 0.37% (95% caudal 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 whereas 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 after multivariable modeling included purebred status (*a priori* interest), neuter status, and body weight 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, $P < .001$) times the odds and dogs aged between 4 and 7 years had 0.22 (95% CI: 0.10–0.48, $P < .001$) 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, $P < .001$) times the odds of CKD of uninsured dogs. Cocker Spaniels (odds ratio [OR] 6.39, 95% CI: 1.63–25.00, $P = .008$) and Cavalier King Charles Spaniels (CKCS) (OR 5.57, 95% CI: 1.07–28.97, $P = .041$) had increased odds of CKD compared with crossbreds. Clustering within the veterinary clinic attended did not improve the model ($P = .4273$). No significant interactions were found. The Hosmer-Lemeshow test indicated good model fit ($P = .7285$). The area under ROC curve was 0.8783, indicating excellent CKD discrimination.[36]

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

Risk Factor	Odds Ratio	95% CI	*P*-Value
Age group (years)			
Under 4	0.06	0.03–0.14	<.001
4 to <7	0.22	0.10–0.48	<.001
7 to <12	Referent	Referent	Referent
Over 12	5.49	2.84–10.60	<.001
Insured status			
Uninsured	Referent	Referent	Referent
Insured	2.55	1.50–4.33	<.001
Breeds (named if ≥12 study dogs)			
Crossbred	Referent	Referent	Referent
Breeds with <12 study dogs	2.58	1.24–5.38	.011
Border Collie	7.65	0.83–70.51	.073
Cavalier King Charles Spaniel[a]	5.57	1.07–28.97	.041
Cocker Spaniel[a]	6.39	1.63–25.00	.008
Jack Russell Terrier	1.56	0.54–4.54	.415
Labrador Retriever	0.53	0.16–1.72	.292
Shih Tzu	1.45	0.26–8.07	.674
Staffordshire Bull Terrier	0.84	0.21–3.46	.815
West Highland White Terrier	1.38	0.36–5.27	.638
Yorkshire Terrier	1.47	0.48–4.52	.506

[a]Individual breed with significantly higher CKD odds than crossbreds.

For dogs aged less than 5 years, purebred/crossbred status was not associated with CKD ($P = .218$).

Comorbid Disorders and Clinical Signs

The most frequent CKD comorbid disorders recorded were gingivitis/periodontitis (69 cases, 30.3%), cardiac disorders (68, 29.8%), and musculoskeletal disorders (56, 24.6%). After adjustment, disorders significantly associated with CKD included hypertension (OR: 25.71, 95% CI 1.38–479.20, $P < .001$) and cardiac disease (OR: 3.88, 95% CI 1.69–8.90, $P < .001$) (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, $P < .001$), anemia (OR: 40.71, 95% CI 2.00–827.66, $P < .001$), weight loss/cachexia (OR: 12.89, 95% CI 4.81–34.55, $P < .001$), polyuria/polydipsia (OR: 7.70, 95% CI 3.53–16.82, $P < .001$), urinary incontinence (OR: 4.97, 95% CI 1.72–14.37, $P < .001$), and vomiting (OR: 4.57, 95% CI 2.53–8.24, $P < .001$) (Table 3).

Survival Analysis

Using a Kaplan-Meier survival curve, the median survival time from CKD diagnosis until death because of CKD (including euthanasia) was 226 days (95% CI 112–326 days). No demographic variables were significantly associated with survival differences, but IRIS stage ($P < .001$) (Fig 1) and blood urea nitrogen concentration ($P < .001$) (Fig 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, $P = .023$) times and dogs in IRIS Stage 4 had 4.71 (95% CI 1.74–12.72, $P = .002$) 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, $P < .001$) 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] that 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 overrepresent 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

Table 3. Comorbid disorders and clinical signs having significant association ($P < .05$) with chronic kidney disease in dogs 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% CI	*P*-Value
Disorder diagnosed					
Hypertension[a]	14 (6.1)	0 (0.0)	25.71	1.38–479.20	<.001
Pancreatitis[a]	11 (4.8)	0 (0.0)	16.96	0.69–414.01	.021
Cardiac disorder	68 (29.8)	13 (5.7)	3.88	1.69–8.90	<.001
Clinical sign					
Halitosis[a]	27 (11.8)	0 (0.0)	57.03	3.16–1030.50	<.001
Anaemia[a]	9 (3.9)	0 (0.0)	40.71	2.00–827.66	<.001
Weight loss/cachexia	66 (28.9)	6 (2.6)	12.89	4.81–34.55	<.001
Polyuria/polydipsia	100 (43.9)	10 (4.4)	7.70	3.53–16.82	<.001
Urinary incontinence	45 (19.7)	5 (2.2)	4.97	1.72–14.37	<.001
Vomiting	114 (50.0)	38 (16.7)	4.57	2.53–8.24	<.001
Appetite decreased/Anorexia	90 (39.5)	26 (11.4)	3.66	1.93–6.94	<.001
Lethargy/depressed	50 (21.9)	21 (9.2)	3.34	1.59–7.02	<.001
Diarrhea/melaena	85 (37.3)	38 (16.7)	2.29	1.26–4.16	.006

[a]Stata *firthlogit* modeling used because of complete separation.

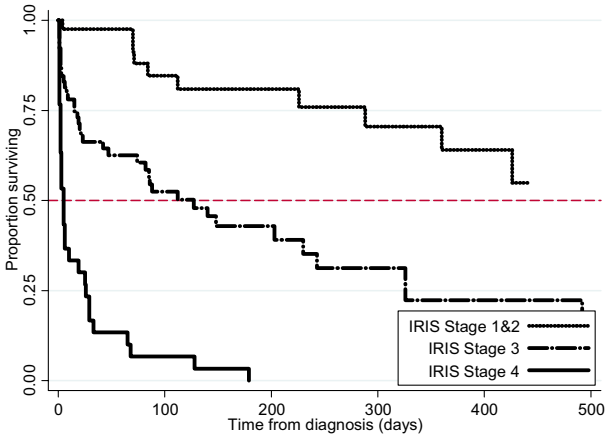

Fig 1. Kaplan-Meier survival curves for dogs diagnosed with chronic kidney disease grouped by International Renal Interest Society (IRIS) stage at diagnosis showing reducing survival with increasing IRIS stage.

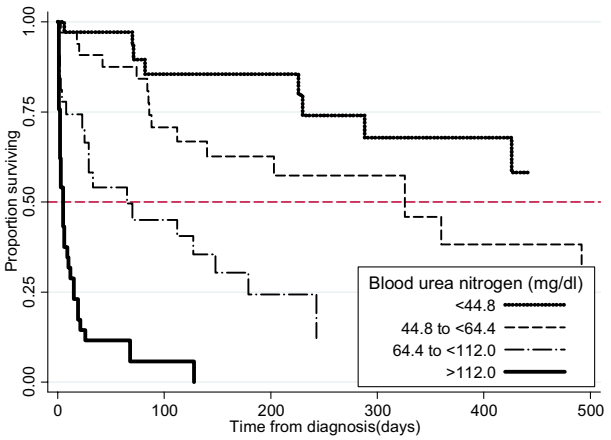

Fig 2. Kaplan-Meier survival curves for dogs diagnosed with chronic kidney disease grouped by blood urea nitrogen concentration (mg/dL) at diagnosis showing reducing survival with increasing blood urea nitrogen concentration.

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 negatives (true cases that are missed) and false positives (noncases 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. This study results estimated CKD TP (0.37%) to be almost twice as high as the 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]

Noninsured animals were less than half as likely to receive a CKD diagnosis as insured animals, agreeing

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	.023
4	30 (22.1)	4.71	1.74–12.72	.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	.659
64.4 to less than 112.0	32 (23.0)	2.60	0.98–6.90	.055
112.0 and above	37 (26.6)	7.76	2.65–22.74	<.001

with Swedish pet insurance analysis where noninsured 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 welfare in dogs 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 hypothesized 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 genealogic 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 (eg, 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 (1.73–6.39) and CKCS (2.72–5.57) because of the younger age distribution and lower insurance status for these breeds relative to many other breeds analyzed (data not shown). This highlights improved interpretation resulting from multivariable analyses that account for confounding effects within epidemiologic studies.

Vigilance for comorbid 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 suboptimal use of blood pressure monitoring among primary practice caseloads.

Although previously identified as an important predictor for CKD in dogs,[14] this 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 reaffirms several previously reported and unpleasant CKD clinical signs (weight loss, polyuria/polydipsia, anemia, urinary incontinence, vomiting, and diarrhea[2,3,14]) establishing CKD as a disorder that can compromise 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 2 occasions in the stable patient, with substaging based on proteinuria and systemic blood pressure. This 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 support their in-practice use for CKD case management and prognosis.[21]

There were some limitations to this study. Although practice selection was a convenience sample mainly in central and southeast England, the high number of participating practices (89) should assure generalizability. Clinical laboratory results were available only when transcribed to the clinical notes, introducing possible transcription error and bias. The inclusion of comorbid disorder diagnoses relied upon the attending veterinarian detecting and recording the concurrent disease. The performance and results of positive tests (eg, a dog has hypertension) may be more likely to be recorded than information related to tests that are found to be negative (eg, a dog does not have hypertension). Case notes without a recorded comorbid 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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References

1. Polzin DJ. Chronic kidney disease in small animals. Vet Clin North Am: Small Anim Pract 2011;41:15–30.

2. Nelson RW, Couto CG. Small Animal Internal Medicine, 4th ed. Edinburgh: Mosby; 2009.

3. Polzin DJ, Osborne CA, Ross S. Chronic kidney disease. In: Ettinger SJ, Feldman EC, eds. Textbook of Veterinary Internal Medicine: Diseases of the Dog and Cat, 6th ed. Stephen J. Ettinger, Edward C. Feldman, eds. St. Louis, MO; Oxford: Elsevier Saunders; 2005:1756–1785.

4. Macdougall DF, Cook T, Steward AP, et al. Canine chronic renal disease: prevalence and types of glomerulonephritis in the dog. Kidney Int 1986;29:1144–1151.

5. Brown SA. Management of chronic kidney disease. In: Elliott J, Grauer GF, eds. BSAVA Manual of Canine and Feline Nephrology and Urology, 2nd ed. Quedgeley: British Small Animal Veterinary Association; 2007:223–230.

6. Sosnar M. Retrospective study of renal failure in dogs and cats admitted to University of Veterinary and Pharmaceutical Sciences Brno during 1999–2001. Acta Veterinaria Brno 2003;72:593–598.

7. Gardner IA. The utility of Bayes' theorem and Bayesian inference in veterinary clinical practice and research. Aust Vet J 2002;80:758–761.

8. Bartges JW. Chronic kidney disease in dogs and cats. Vet Clin North Am: Small Anim Pract 2012;42:669–692.

9. Lees GE. Early diagnosis of renal disease & renal failure. Vet Clin North Am: Small Anim Pract 2004;34:867–885.

10. Grauer GF. Early detection of renal damage and disease in dogs and cats. Vet Clin North Am: Small Anim Pract 2005;35:581–596.

11. Tenhündfeld J, Wefstaedt P, Nolte IJA. A randomized controlled clinical trial of the use of benazepril and heparin for the treatment of chronic kidney disease in dogs. J Am Vet Med Assoc 2009;234:1031–1037.

12. Müller-Peddinghaus R, Trautwein G. Spontaneous glomerulonephritis in dogs: II. Correlation of glomerulonephritis with age, chronic interstitial nephritis and extrarenal lesions. Vet Pathol 1977;14:121–127.

13. Vaden SL. Glomerular disease. Top Companion Anim Med 2011;26:128–134.

14. Bartlett PC, Van Buren JW, Bartlett AD, et al. Case-control study of risk factors associated with feline and canine chronic kidney disease. Vet Med Int 2010;2010:1242–1249.

15. DiBartola SP, Tarr MJ, Webb DM, et al. Familial renal amyloidosis in Chinese Shar Pei dogs. J Am Vet Med Assoc 1990;197:483–487.

16. Jones BR, Gething MA, Badcoe LM, et al. Familial progressive nephropathy in young Bull Terriers. N Z Vet J 1989;37:79–82.

17. Lees G, Helman R, Homco L, et al. Early diagnosis of familial nephropathy in English Cocker Spaniels. J Am Anim Hosp Assoc 1998;34:189–195.

18. McAloose D, Casal M, Patterson DF, et al. Polycystic kidney and liver disease in two related West Highland White Terrier litters. Vet Pathol 1998;35:77–80.

19. Chandler ML, Elwood C, Murphy KF, et al. Juvenile nephropathy in 37 Boxer dogs. J Small Anim Pract 2007;48:690–694.

20. Glickman LT. Association between chronic azotemic kidney disease and the severity of periodontal disease in dogs. Prev Vet Med 2011;99:193–200.

21. IRIS. International Renal Interest Society (IRIS). Available at: http://www.iris-kidney.com/index.shtml. Novartis Animal Health Inc.; 2007. Accessed March 8, 2012.

22. Elliott J. Staging chronic kidney disease. In: Elliott J, Grauer GF, eds. BSAVA Manual of Canine and Feline Nephrology and Urology, 2nd ed. Quedgeley: British Small Animal Veterinary Association; 2007:161–166.

23. VetCompass. VetCompass: Health surveillance for UK companion animals. Available at: http://www.rvc.ac.uk/VetCompass. RVC Electronic Media Unit; 2012. Accessed March 20, 2012.

24. Haahr M. RANDOM.ORG: True random number service. Available at: http://www.random.org/TSDA; 2012. Accessed March 20, 2012.

25. Epi Info 7 CDC. Centers for Disease Control and Prevention (US): Introducing Epi Info 7. Available at: http://wwwn.cdc.gov/epiinfo/7. Atlanta, GA: CDC; 2012. Accessed March 12, 2012.

26. The VeNom Coding Group. VeNom Veterinary Nomenclature. Available at: http://www.venomcoding.orgVeNom Coding Group; 2012. Accessed March 12, 2012.

27. Upjohn M, Jasani S, Church D, et al. Establishing an Electronic Patient Record (EPR) in first opinion veterinary practice: Challenges to overcome. In: Society for Veterinary Epidemiology and Preventive Medicine (SVEPM). Liverpool 2008;1–1.

28. The Kennel Club. Kennel Club's Breed Information Centre. Available at: http://www.the-kennel-club.org.uk/services/public/breed/Default.aspx. London: The Kennel Club; 2012. Accessed May 15, 2012.

29. Thomas A, O'Hara B, Ligges U, et al. Making BUGS open. R News 2006;6:12–17.

30. Thomas A. OpenBUGS. Available at: http://www.openbugs.info/w/FrontPage. Helsinki: 2009. Accessed May 15, 2012.

31. McV Messam LL, Branscum AJ, Collins MT, et al. Frequentist and Bayesian approaches to prevalence estimation using examples from Johne's disease. Anim Health Res Rev 2008;9:1–23.

32. Su C-L. Bayesian Epidemiologic Screening Techniques: Betabuster. Davis, US: Department of Medicine and Epidemiology, University of California, Davis; 2012.

33. Dohoo I, Martin W, Stryhn H. Veterinary Epidemiologic Research, 2nd ed. Charlottetown, Canada: VER Inc; 2009.

34. Kirkwood BR, Sterne JAC, Kirkwood B. Essential Medical Statistics, 2nd ed. Kirkwood BR, Sterne JAC, eds. Malden, MA; Oxford: Blackwell Science; 2003.

35. Heinze G, Schemper M. A solution to the problem of separation in logistic regression. Stat Med 2002;21:2409–2419.

36. Hosmer DW, Lemeshow S. Assessing the fit of the model. In: Applied Logistic Regression. New York, NY: John Wiley & Sons; 2000.

37. Bartlett PC, Van Buren JW, Neterer M, et al. Disease surveillance and referral bias in the veterinary medical database. Prev Vet Med 2010;94:264–271.

38. Drobatz KJ. Measures of accuracy and performance of diagnostic tests. J Vet Cardiol 2009;11:S33–S40.

39. Doherr MG, Audigé L. Monitoring and surveillance for rare health-related events: A review from the veterinary perspective. Philos Trans R Soc Lond B Biol Sci 2001;356:1097–1106.

40. Bartges J, Polzin DJ. Nephrology and Urology of Small Animals. Oxford: Wiley-Blackwell; 2011.

41. Egenvall A, Nodtvedt A, Penell J, et al. Insurance data for research in companion animals: Benefits and limitations. Acta Vet Scand 2009;51:42.

42. Elliott J, Watson ADJ. Chronic kidney disease: Staging and management. In: Bonagura JD, Kirk RW, eds. Kirk's Current Veterinary Therapy, XIV. Philadelphia, PA; London: Elsevier Saunders; 2008:883–892.

43. DiBartola SP. Chapter 264: Familial renal disease in dogs and cats. In: Ettinger SJ, Feldman EC, eds. Textbook of Veterinary Internal Medicine : Diseases of the Dog and Cat, 6th ed. St. Louis, MO; Oxford: Elsevier Saunders; 2005:1819–1824.

44. Chen ZJ. Molecular mechanisms of polyploidy and hybrid vigor. Trends Plant Sci 2010;15:57–71.

45. Van Vleck LD, Pollak EJ, Oltenacu EAB. Genetics for the Animal Sciences. New York, NY: W.H. Freeman; 1987.

46. Liberg O, Andrén H, Pedersen H-C, et al. Severe inbreeding depression in a wild wolf *Canis lupus* population. Biol Lett 2005;1:17–20.

47. Oliver JAC, Gould DJ. Survey of ophthalmic abnormalities in the Labradoodle in the UK. Vet Rec 2012;170:390.

48. Schiffrin EL, Lipman ML, Mann JFE. Chronic kidney disease: Effects on the cardiovascular system. Circulation 2007;116:85–97.

49. Bronden LB, Nielsen SS, Toft N, et al. Data from the Danish Veterinary Cancer Registry on the occurrence and distribution of neoplasms in dogs in Denmark. Vet Rec 2010;166:586–590.

50. Ling GV, Ruby AL, Johnson DL, et al. Renal calculi in dogs and cats: Prevalence, mineral type, breed, age, and gender interrelationships (1981–93). J Vet Intern Med 1998;12:11–21.

51. Nicolle AP, Chetboul V, Allerheiligen T, et al. Azotemia and glomerular filtration rate in dogs with chronic valvular disease. J Vet Intern Med 2007;21:943–949.

52. Bartges JW, Willis AM, Polzin DJ. Hypertension and renal disease. Vet Clin North Am Small Anim Pract 1996;26:1331–1345.

53. Lund EM, Armstrong PJ, Kirk CA, et al. Health status and population characteristics of dogs and cats examined at private veterinary practices in the United States. J Am Vet Med Assoc 1999;214:1336–1341.

54. Gregory NG. Physiological mechanisms causing sickness behaviour and suffering in diseased animals. Anim Welfare 1998;7:293–305.

55. Marinelli L, Adamelli S, Normando S, et al. Quality of life of the pet dog: Influence of owner and dog's characteristics. Appl Anim Behav Sci 2007;108:143–156.