Chronic kidney disease in cats attending primary-care practice in the UK: A VetCompass™ study

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This works conforms to the STROBE guidelines for reporting observational epidemiological studies.

INTRODUCTION

Chronic kidney disease (CKD) is a commonly recognised heterogeneous disease syndrome in cats, with previous studies estimating a prevalence of 1.7% to 3.6% in cats attending primary-care practice in the UK [1,2]. Prevalence increases with age, with up to 80% of cats aged over 15 years estimated to have CKD in some studies [3–5]. Kidney disease has also been reported as the most common cause of death in cats over 5 years of ages in the UK, with almost 1 in 7 animals dying of this condition[6]. Previously reported median survival time estimates ranged from 21 days to 1151 days depending on severity of renal dysfunction at diagnosis [7–9].

It has previously been reported that CKD does not become clinically apparent until around 75% of the renal function has been lost [10]. Though as the condition progresses, considerable morbidity has been reported, with cats experiencing a range of clinical signs as the disease progresses. The most commonly described clinical signs were polydipsia, weight loss, anorexia, polyuria, depression, and vomiting [8,11,12], with anorexia, weight loss and depression all reported to negatively impact on the quality of life of the cat [13].

Previously reported risk factors for CKD diagnosis include age [8,11,14], sex [15,16], breed [11,15], hyperthyroidism [17,18], feline leukaemia virus (FeLV) [19,20] and feline immunodeficiency virus (FIV) [21,22]. Vaccination [23] and incomplete recovery from acute kidney injury [24] have additionally been hypothesised as other potential risk factors. Useful prognostic indicators following diagnosis include proteinuria [25–27], the feeding of a low protein, low phosphate diet [9,28], anaemia [25,27,29] and serum phosphate levels [25,27,29]. No single variable has been identified that reliably predicts survival following diagnosis of CKD. This may be due to the heterogeneous nature of CKD in cats and the variable rates of progression observed [27].

Clinically apparent CKD causes considerable morbidity and mortality in cats. Additionally, up to 15% of apparently healthy cats aged 10 years or older are found to have undiagnosed CKD at a routine

health check [30,31], suggesting that CKD may result in morbidity to a substantial proportion of the geriatric cat population. Previous research on risk factors for CKD diagnosis and survival following diagnosis of CKD has been limited mainly to referral populations, prospective research following standard protocols focussing on one region (London) and questionnaire based studies, with little work undertaken using general primary-care data. This may reduce the generalisability of the results to the wider cat population[32]. This study aimed to estimate prevalence and risk factors for CKD diagnosed in cats attending VetCompass™ practices in the UK, to document the current standard of care applied in these practices and to evaluate survival following CKD diagnosis. By comparison with published expert recommendations (guidelines), these data should assist primary practitioners identify ways in which diagnosis and management of feline CKD could be improved.

MATERIALS AND METHODS

Ethics approval was provided by the Royal Veterinary College Clinical Research Ethical Review Board (URN M2015 0050).

Data collection and management

VetCompass™ collects and collates anonymised electronic patient records (EPR) from enrolled primary-care veterinary practices in the UK. Patient demographic (species, breed, date of birth, sex, neutering status, bodyweight) and clinical data (free clinical text, VeNom [33] diagnosis terms and treatment fields) are uploaded for use in research studies[1,34].

A stratified prevalence study derived from the cohort of cats attending 244 participating VetCompass™ practices from 1st January 2012 to 31st December 2013 was used to estimate the two-year period prevalence [35]. A frequency matched case control study, nested within the study cohort, was used to investigate risk factors for diagnosis of CKD and a retrospective cohort study was used to explore survival following CKD diagnosis. The sampling protocol for the three studies is illustrated in Figure 1. Potential cases of CKD were identified by searching the EPR for VeNom diagnosis codes (renal failure, renal disorder, renal disease, chronic renal failure, renal insufficiency),

74 treatment (KD, RCW feline renal, renal food, renalzin, ipakitine, alucap, semintra, tumil K, renal
75 profile, UPC) and free text clinical terms (CKD, CRD, CRF, chronic renal/kidney
76 failure/disease/insufficiency, kidney disease, renal disease, iris stage). The results from all searches
77 were merged and duplicates removed. A random sample of 20% of potential cases was selected to
78 review in detail the EPRs manually. The case definition required a diagnosis of CKD (or synonym)
79 recorded within the EPR, or a diagnosis of kidney disease (or synonym) within the EPR with evidence
80 of chronicity of disease, with chronicity defined as the presence of clinical signs or azotaemia for ≥3
81 months. 'Pre-existing cases' were those first diagnosed prior to the study period and 'incident cases'
82 were those first diagnosed during the study period. Controls were identified by examining EPR
83 records of a random sample of cats not identified as potential cases in the EPR CKD searches.
84 Controls were required to have not had CKD suspected at any time within the EPR. Controls selected
85 that were hyperthyroid needed to have been non-azotaemic when total T4 levels were less than
86 40nmol/l [36] to be included in the study. Cases and controls were frequency matched by age (< 9
87 years and ≥ 9 years) to control for the effect of age.

88 Demographic data were extracted automatically from the database, and further clinical data were
89 extracted manually from the EPR (date of diagnosis, death, reason for presentation at diagnosis,
90 clinical signs and physical exam results, laboratory results, imaging results, blood pressure
91 measurement, vaccination history, historical exposure to potential nephrotoxic drugs and toxins,
92 treatments prescribed and co-morbidities). Data were exported to Microsoft Excel 13 for cleaning
93 and then further exported to Stata 11 (StataCorp LP, College Station, TX) for statistical analysis.

94 Sample size calculations indicated that at least 290 cases and 290 controls would be required to be
95 sampled to detect an odds ratio of 2 or greater for a risk factor present in 10% of controls, assuming
96 80% power and 95% confidence [37]

97 Medians and interquartile ranges (IQR) were calculated for continuous variables. Age was
98 categorised as < 9 years or ≥ 9 years. Bodyweight was categorised into quintiles and also maintained

as a continuous variable. Breed was categorised into crossbred and purebred, with purebred being a recorded breed name recognised by International Cat Care [38]. Reason for presentation at CKD diagnosis was categorised as clinical signs, geriatric health check (apparently healthy cats aged ≥ 7 years presented for a health check) and monitoring of pre-existing disease. Serum creatinine and serum phosphate at diagnosis were categorised based on IRIS guidelines [39] and maintained as continuous variables. Vaccination was categorised as annual, kitten only or non-annual and no recorded vaccination in the full EPR. Non-steroidal anti-inflammatory drug (NSAID) use was categorised into one-off treatment, repeated one-off treatment and long term treatment recorded in the full EPR. Days since last anaesthetic was categorised into 0 – 179 days, 180 – 364 days and no anaesthetic recorded in 365 days prior to CKD diagnosis.

Statistical Analysis

The prevalence of CKD was estimated from the cohort of cats attending VetCompass™ practices during the study period. A stratified analysis was used to describe the incidence risk and prevalence of CKD in the VetCompass™ cat population, with the estimates adjusted for the random sampling of 20% of potential CKD cases (Fig. 1) [35]. Stratum 1 contained the cats that had been identified with the search terms and had their EPR read in detail and had a confirmed case/ non-case status. Stratum 2 contained all the cats that were not identified with the search terms, and were assumed to be non-cases. A probability weighting was ascribed to each stratum (1/the proportion of the group that had a confirmed case or non-case status) to account for the different proportions of all cats included [40]. All 'pre-existing' and 'incident' cases were included in prevalence estimates.

In the case-control study all incident cases were included in the analysis and compared to frequency age-matched controls. Multivariable logistic regression was used to identify risk factors associated with CKD diagnosis. Cats that had no age recorded were removed from the analysis. Variables that were broadly associated with diagnosis of CKD ($p < 0.2$) in the univariable analysis were carried forward to the multivariable model. Age was forced into the model to control for the frequency

matched sampling strategy. Model fit was assessed using the Hosmer-Lemeshow test [41] and predictive ability was assessed by examining the area under the ROC curve [42]. The model was adjusted for veterinary group attended as a confounder by inclusion as a variable in the final model. Statistical significance was set at the 5% level.

All incident cases identified had their clinical notes followed until 31st December 2015. Cats with one day or more follow up were included in the survival analysis. Median survival time and mortality rates were estimated. Multivariable Cox proportional hazards modelling was used to investigate risk factors associated with survival following CKD diagnosis. Variables broadly associated with survival at the univariable level ($p < 0.2$) were carried forward to the multivariable model assessment. Proportionality of hazards was confirmed by assessing the Schoenfeld residuals and the Kaplan-Meier curve. Model fit was assessed by examining the Cox-Snell residuals and predictive ability of the model was assessed using Harrell's C concordance statistic [42]. The model was adjusted for veterinary group attended as a confounder by inclusion as a variable in the final model. Statistical significance was set at the 5% level.

RESULTS

The denominator population included 353,448 cats attending 244 VetCompass™ clinics during the study period. EPR searches identified 11,836 potential cases, of which 2,368 (20%) were reviewed in detail and 625 were classified as incident and 336 pre-existing cases. Overall CKD prevalence was estimated at 1.2% (95% confidence interval (CI) 1.1% - 1.3%). Prevalence increased with age: 0.1% (95% CI 0.1% - 0.2%) in cats < 9 years and 3.6% (95% CI 3.3% - 3.8%) in cats aged ≥ 9 years (Table 1). CKD prevalence by breed was highest in Burmese cats (5%, see Table 1).

148 Descriptive statistics

149 Sex was recorded in 98.3% of cats, neuter status in 72.0% of cats and bodyweight in 43.8% of cats.
150 Age was not recorded in 8 cases and 8 controls. Median age at diagnosis of CKD was 14.8 years (IQR
151 12.1 – 16.7).

152 Cats were most commonly diagnosed with CKD following presentation to the veterinary surgeon due
153 to clinical signs compatible with CKD (66.6%; 416). Diagnosis followed a geriatric health or pre-
154 anaesthetic check in only 10.6% (66) and 7.0% (44) of cases respectively. Weight loss (49.9%; 311),
155 polydipsia (38.6%; 241) and polyuria (24.5%; 153) were the most frequently reported clinical signs.
156 At diagnosis, over half of cats (56.6%; 354) had two or more compatible clinical signs recorded, and
157 24.8% (155) cats had no clinical signs recorded. Diagnosis was confirmed using combined
158 biochemistry and urine analysis in 52.6% (329) of cats, with 33.9% (212) confirmed with
159 biochemistry, 3.5% (21) confirmed with urinalysis and 10.1% (63) diagnosed following clinical
160 examination alone. At diagnosis, 14.4% (90) had urine protein: creatinine ratio (UPC) performed and
161 11.4% (71) had imaging. IRIS staging[39] was recorded in the EPR of 19.8% (124), with 22.6% (28) in
162 stage one, 46.8% (58) in stage two, 26.3% (74) in stage three and 14.6% (41) in stage four. Serum
163 creatinine was recorded in the EPR of 45.0% (281). When categorised by serum creatinine
164 concentration, 5.3% (15) were in IRIS stage one, 53.7% (151) in stage two, 26.3% (74) in stage three
165 and 14.6% (41) in stage four at diagnosis. During monitoring, repeated biochemistry was carried out
166 in 32.6% (204) of cats and blood pressure measured in 25.6% (160). Just over half (51.2%; 83) of
167 those CKD cases where blood pressure was measured were co-morbidly diagnosed with
168 hypertension.

169 The most common treatment prescribed to cats diagnosed with CKD was a proprietary renal diet
170 (63.2%; 395) (Table 2). Just over a fifth of cats (22.8%; 142) had no recorded treatment for CKD, with
171 over half of these (54.9%; 78) being euthanised within 7 days of CKD diagnosis.

Risk factor analysis

The following variables were found to be broadly associated ($p < 0.2$) with incident CKD diagnosis and carried forward to the multivariable analysis: bodyweight, breed, heart auscultation abnormality, presence of goitre, vaccination, NSAID treatment, days since previous anaesthetic, hyperthyroidism, arthritis, cystitis, and hepatopathy (all diagnosed prior to CKD).

Cats with no age recorded were excluded from multivariable analysis (8 cases and 8 controls). Table 3 reports the risk factors associated with diagnosis of CKD in the multivariable analysis. Hyperthyroid cats, purebred cats, the absence of a recorded goitre, the presence of a heart auscultation abnormality, long term NSAID treatment, no cardiomyopathy diagnosis, no anaesthetic within one year of diagnosis and a bodyweight < 3.5kg at diagnosis were all associated with increased risk of CKD diagnosis (Table 3). The model had good fit (Hosmer-Lemeshow p=0.46) and good predictive ability (area under the ROC curve 0.81).

Survival analysis

Three hundred and eighty (60.8%) cats had death recorded in the EPR during the follow up to the end of 2015; with 90.3% (343) of these cats being euthanised. The most frequently recorded reason for euthanasia included CKD (37.9%; 144) and poor quality of life (22.6%; 86). A third (35.8%; 224) of cats were lost to follow up. Ninety two cats were not seen by a vet following first diagnosis of CKD, most of which (82.6%; 76) were euthanised at diagnosis. Of these cats, 40.8% (31) had biochemistry performed. Of the 15 cats with serum creatinine concentration recorded in their EPR, 66.7% (10) were in IRIS stage 4 CKD.

All-cause mortality rate was calculated as 8.1 deaths per 10.0 CKD cat years at risk (95% CI 7.3 – 9.0).

The 92 cats that were not seen after diagnosis were excluded from further analysis as, from a clinical perspective, they would not aid any further understanding of prediction of disease progression or treatment effectiveness.

Median survival time in cats with at least one day follow up was 388 days following diagnosis of CKD (IQR 88 – 1042 days) (Fig. 2). The following variables were broadly associated ($p < 0.2$) with survival of at least one day following CKD diagnosis at the univariable level: neuter status, breed, bodyweight, reason for presentation, method of diagnosis, heart auscultation, blood pressure, IRIS stage at diagnosis, serum phosphate at diagnosis, UPC at diagnosis, treatments used (renal diet, phosphate binders, potassium supplementation, amlodipine, anabolic steroids, IVFT) , and diagnosis of; periodontal disease, cystitis, cardiomyopathy, hepatopathy, constipation and diabetes mellitus.

Table 4 details the associations identified with survival of at least one day following CKD diagnosis in the multivariable Cox proportional hazards model. Serum phosphate at diagnosis, UPC at diagnosis, breed, proprietary diet prescription, IVFT, diagnosis of constipation, body-weight, phosphate binder prescription and cystitis diagnosis were all associated with survival. An interaction with time was identified with the association between serum phosphate at diagnosis and survival. The association of serum phosphate with survival was only identified in the first 400 days following diagnosis of CKD. Proportionality of hazards was met (Scaled schoenfeld residuals p=0.22) and the model had good predictive ability (Harrell's C = 0.85).

DISCUSSION

This study is the largest to date investigating the prevalence of, and risk factors for, CKD diagnosis and survival following diagnosis in cats attending primary-care practices in the UK. Prevalence of CKD in cats attending VetCompass™ practices was estimated as 1.2% (95% CI 1.1% - 1.3%) increasing to 3.6% (95% CI 3.3% - 3.8%) in cats aged ≥ 9 years. The large size of the study population suggests that this prevalence value is likely to be reasonably generalizable to the UK primary-practice attending cat population. The overall prevalence was 6 times higher than the prevalence previously reported in dogs from the same database, and the median survival time following diagnosis in cats was found to be 1.7 times that in dogs, suggesting that CKD results in a greater burden of disease in cats than dogs in primary-care practice due to both higher prevalence and duration [34].

In the current study, most cats (66%) were diagnosed with CKD once clinical signs were present, with many cats showing two or more clinical signs at diagnosis. It has previously been reported that clinical signs of CKD do not occur until at least 75% of kidney function has been lost [10]. This suggests that CKD is underdiagnosed in this population, as those cats with sub-clinical disease may be missed. This conclusion is supported by the limited number of diagnoses made during geriatric health checks, despite previous evidence that up to 15% of apparently healthy geriatric cats have evidence of CKD after biochemistry and urinalysis [31] and up to 30% of geriatric cats develop azotaemia within 12 months [14,23]. The limited proportion of cats diagnosed following a health check suggests that these are not carried out routinely, indicating there may be many older cats that have undiagnosed subclinical CKD. This could impact on morbidity and cause a reduction in quality of life associated with CKD, as earlier diagnosis allows for early implementation of treatments that can slow progression of disease, limiting development of clinical signs [43].

Monitoring of cats diagnosed with CKD was limited in the current study, with a minority of cats receiving repeated biochemistry tests, UPC analyses or BP measurements. This is consistent with findings from a study on monitoring of hyperthyroidism in cats in the UK and a questionnaire response from owners of cats with CKD [12,44] , despite recommendations to monitor azotaemia, BP and UPC following CKD diagnosis [39,45]. Cats with CKD have been found to have 5 times the risk of developing hypertension in comparison to cats without CKD [46]. It is important to identify hypertension early to instigate treatment to reduce the risk of target organ damage and its associated morbidity [47]. The limited use of blood pressure measurement indicates that this group of CKD cats may be at increased morbidity risk from hypertension secondary to CKD. It was not possible to extract information from the EPR on whether the decision to not perform these investigations was owner or veterinary dependent, or both. Further study into the decision-making process would aid targeted education for improved monitoring of CKD.

In the current study, risk factors associated with CKD diagnosis were similar to those previously identified in other populations, with purebred status[11,15] and hyperthyroid status[18,48] found to be associated with CKD diagnosis. The current study is the first to identify long-term NSAID therapy as a risk factor for CKD. A possible explanation for this is chronic low-level nephrotoxicity causing kidney injury that leads to CKD [49,50]. It is also possible that cats on long-term NSAID therapy represents a form of diagnostic bias because these cats are more likely to receive blood tests than cats not receiving therapy. The protective association found in the current study between a recent anaesthetic and CKD diagnosis is inconsistent with previous research [15]. It is plausible that this association is a form of reverse causality whereby veterinary surgeons opt to avoid anaesthesia on cats they consider to be at risk of CKD. The association identified between low bodyweight and CKD diagnosis is likely to indicate reverse causality, as cats diagnosed with CKD are likely to have lost weight in the months leading up to diagnosis[8].

Vaccination [23], periodontal disease [15,23] and cystitis [15] have previously been reported as risk factors for CKD diagnosis, but were not identified as such in the current study. Differences in study design, study population and methods of data collection and recording are likely to explain why these previously identified risk factors for CKD were not identified by the present study.

Similarly to the risk factor analysis, a number of variables found to be associated with survival have been previously identified, including serum phosphate concentration [7,27], proteinuria [25,26] and the use of a proprietary renal diet [9,28,43]. Serum phosphate concentration was only predictive in the first 400 days following diagnosis. This is logical given the mainstay of CKD treatment is reduction of phosphate through proprietary diets and oral phosphate binders, so a single measurement of serum phosphate concentration at diagnosis of CKD is unlikely to be predictive of survival once is successfully implemented.

The other variables associated with survival were likely related to disease severity at diagnosis (bodyweight [8], IVFT [8] and constipation [51,52]), or were related to owner management of the cat. It is

possible that owners of purebred cats are more likely to pursue investigations and treatments for their cats in comparison to owners of crossbred cats, or that purebred cats may be more likely to be insured, although insurance status has not been shown to be associated with longevity in previous studies [6]. As cystitis is usually a chronic disease in cats, cystitis cases may have more frequent veterinary visits and therefore receive improved veterinary care compared to cats that visited less frequently.

There were limitations to the present study. The data were not collected for research purposes, so information may have been inconsistently recorded in all EPRs (i.e. high missing-ness). This was particularly evident for blood test results and possibly resulting in serum creatinine levels and PCV not being associated with survival, despite being previously identified as strong risk factors [25,26,29]. To ensure adequate power, cats with missing data for these variables were retained in the analyses. The case definition relied on the veterinary surgeons to correctly diagnose CKD rather than a strict definition based on biochemical markers. It is possible that some misclassification of cases could have occurred. Insurance data were not available for this study. Insurance status has been identified as a risk factor for diagnosis of other conditions, so may be a confounder for some of the variables in the final models [34,53]. As a third of cats were lost to follow up, it is possible that there was bias within the survival estimates. Some of the cats lost to follow up may have died at home or were euthanised at another practice, although it is common for owners to notify veterinary practices of death as most practices send notifications for routine check-ups required.

In conclusion, CKD appears to be diagnosed relatively late in the course of the disease in primary care practice. Most cats are diagnosed once clinical signs are present, while monitoring following CKD diagnosis is limited. Increased uptake of routine screening of higher risk cats using urinalysis and biochemistry may identify cats with pre-clinical CKD before clinical signs appear, allowing earlier intervention and a reduction in morbidity and mortality associated with CKD by the application of treatments aimed at slowing progression of the disease. Improved BP monitoring could aid

295 reduction in co-morbidity associated with hypertension and target organ damage. These findings can
296 aid the improved management, health and welfare of CKD cats in primary-care practice.

297

298 REFERENCES

299 1. O'Neill DG, Church DB, McGreevy PD, Thomson PC, Brodbelt DC. Prevalence of disorders
300 recorded in cats attending primary-care veterinary practices in England. Vet J. 2014
301 Nov;202(2):286–91.

302 2. Sanchez-Vizcaino F, Radford A., Newman J, Jones P., Batchelor D, Menacere T, et al.
303 Preliminary charaterisation of the cat consultations presenting with renal disease in small
304 animal practices of the UK through SAVSNET, the Small Animal Veterinary Surveillance
305 Network. In: Boehringer Ingelheim: International Renal and Renovascular Symposium. 2015.
306 p. 52.

307 3. Bartges JW. Chronic Kidney Disease in Dogs and Cats. Vet Clin North Am - Small Anim Pract
308 [Internet]. 2012;42(4):669–92. Available from: http://dx.doi.org/10.1016/j.cvsm.2012.04.008

309 4. Kraweic DR, Gelberg HB. Chronic Renal Disease in Cats. In: Kirk R, editor. Current Veterinary
310 Therapy X [Internet]. Philadelphia: Saunders Elsevier; 1989. p. 1170–3.

311 5. Marino CL, Lascelles BDX, Vaden SL, Gruen ME, Marks SL. Prevalence and classification of
312 chronic kidney disease in cats randomly selected from four age groups and in cats recruited
313 for degenerative joint disease studies. J Feline Med Surg [Internet]. 2014 Jun 1;16(6):465–72.
314 Available from: http://jfm.sagepub.com/lookup/doi/10.1177/1098612X13511446

315 6. O'Neill DG, Church DB, McGreevy PD, Thomson PC, Brodbelt DC. Longevity and mortality of
316 cats attending primary care veterinary practices in England. J Feline Med Surg. 2015 Feb
317 1;17(2):125–33.

318 7. Boyd LM, Langston C, Thompson K, Zivin K, Imanishi M. Survival in Cats with Naturally
319 Occurring Chronic Kidney Disease (2000-2002). J Vet Intern Med [Internet]. 2008
320 Sep;22(5):1111–7. Available from: http://doi.wiley.com/10.1111/j.1939-1676.2008.0163.x

8. Elliott J, Barber PJ. Feline chronic renal failure: clinical findings in 80 cases diagnosed between 1992 and 1995. J Small Anim Pract [Internet]. 1998 Feb [cited 2015 Oct 12];39(2):78–85. Available from: http://doi.wiley.com/10.1111/j.1748-5827.1998.tb03598.x

9. Elliott J, Rawlings JM, Markwell PJ, Barber PJ. Survival of cats with naturally occurring chronic renal failure: effect of dietary management. J Small Anim Pract [Internet]. 2000 Jun [cited 2016 Jan 21];41(6):235–42. Available from: http://doi.wiley.com/10.1111/j.1748-5827.2000.tb03932.x

10. Brown SA, Crowell WA, Brown CA, Barsanti JA, Finco DR. Pathophysiology and Management of Progressive Renal Disease. Vet J. 1997;154:93–109.

11. Lulich JP, Osborne CA, O'Brien TD, Polzin DJ. Feline renal failure: Questions, Answers, Questions. Compend Contin Educ. 1992;14(2):127–52.

12. Caney SM. An online survey of dietary and phosphate binder practices of owners of cats with chronic kidney disease. J Feline Med Surg [Internet]. 2016 Oct 17; Available from: http://jfm.sagepub.com/lookup/doi/10.1177/1098612X16672999

13. Bijsmans ES, Jepson RE, Syme HM, Elliott J, Niessen SJM. Psychometric Validation of a General Health Quality of Life Tool for Cats Used to Compare Healthy Cats and Cats with Chronic Kidney Disease. J Vet Intern Med [Internet]. 2016 Jan [cited 2016 Nov 30];30(1):183–91. Available from: http://doi.wiley.com/10.1111/jvim.13656

14. Jepson RE, Brodbelt D, Vallance C, Syme HM, Elliott J. Evaluation of predictors of the development of azotemia in cats. J Vet Intern Med. 2009;23(4):806–13.

15. Greene JP, Lefebvre SL, Wang M, Yang M, Lund EM, Polzin DJ. Risk factors associated with the development of chronic kidney disease in cats evaluated at primary care veterinary hospitals. J Am Vet Med Assoc [Internet]. 2014 Feb;244(3):320–7. Available from:

http://avmajournals.avma.org/doi/abs/10.2460/javma.244.3.320

16. White J, Norris J, Baral R, Malik R. Naturally-occurring chronic renal disease in Australian cats: a prospective study of 184 cases. Aust Vet J [Internet]. 2006 Jun [cited 2016 Jan 21];84(6):188–94. Available from: http://doi.wiley.com/10.1111/j.1751-0813.2006.tb12796.x

17. van Hoek I, Lefebvre HP, Peremans K, Meyer E, Croubels S, Vandermeulen E, et al. Short- and long-term follow-up of glomerular and tubular renal markers of kidney function in hyperthyroid cats after treatment with radioiodine. Domest Anim Endocrinol. 2009;36(June 2008):45–56.

18. Williams TL, Peak KJ, Brodbelt D, Elliott J, Syme HM. Survival and the development of azotemia after treatment of hyperthyroid cats. J Vet Intern Med. 2010;24(4):863–9.

19. Beatty J. Viral causes of feline lymphoma: retroviruses and beyond. Vet J [Internet]. 2014 Aug [cited 2016 Feb 3];201(2):174–80. Available from: http://www.sciencedirect.com/science/article/pii/S1090023314002238

20. Glick AD, Horn RG, Holscher M. Characterization of feline glomerulonephritis associated with viral-induced hematopoietic neoplasms. Am J Pathol [Internet]. 1978 Aug [cited 2016 Jan 14];92(2):321–32. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2018289&tool=pmcentrez&rendertype=abstract

21. Baxter KJ, Levy JK, Edinboro CH, Vaden SL, Tompkins MB. Renal Disease in Cats Infected with Feline Immunodeficiency Virus. J Vet Intern Med. 2012;26(2):238–43.

22. Poli A, Tozon N, Guidi G, Pistello M. Renal Alterations in Feline Immunodeficiency Virus (FIV)-Infected Cats: A Natural Model of Lentivirus-Induced Renal Disease Changes. Viruses [Internet]. 2012;4(12):1372–89. Available from: http://www.mdpi.com/1999-4915/4/9/1372/

367 23. Finch NC, Syme HM, Elliott J. Risk Factors for Development of Chronic Kidney Disease in Cats.
368 J Vet Intern Med [Internet]. 2016 Mar;30(2):602–10. Available from:
369 http://doi.wiley.com/10.1111/jvim.13917

370 24. Reynolds BS, Lefebvre HP. Feline CKD: Pathophysiology and risk factors - what do we know? J
371 Feline Med Surg. 2013;15(S1):3–14.

372 25. King JN, Tasker S, Gunn-Moore D a, Strehlau G. Prognostic factors in cats with chronic kidney
373 disease. J Vet Intern Med [Internet]. 2007;21(5):906–16. Available from:
374 papers2://publication/uuid/841BE806-ABD9-4680-9B58-6FE81FF9E296

375 26. Syme HM, Markwell PJ, Pfeiffer D, Elliott J. Survival of cats with naturally occurring chronic
376 renal failure is related to severity of proteinuria. J Vet Intern Med. 2006;20:528–35.

377 27. Chakrabarti S, Syme HM, Elliott J. Clinicopathological Variables Predicting Progression of
378 Azotemia in Cats with Chronic Kidney Disease. J Vet Intern Med. 2012;26(2):275–81.

379 28. Plantinga E a, Everts H, Kastelein a MC, Beynen a C. Retrospective study of the survival of
380 cats with acquired chronic renal insufficiency offered different commercial diets. Vet Rec.
381 2005;157:185–7.

382 29. Kuwahara Y, Ohba Y, Kitoh K, Kuwahara N, Kitagawa H. Association of laboratory data and
383 death within one month in cats with chronic renal failure. J Small Anim Pract [Internet]. 2006
384 Aug [cited 2015 Dec 17];47(8):446–50. Available from:
385 http://www.ncbi.nlm.nih.gov/pubmed/16911112

386 30. Lundbol S. Prevalence study on chronic kidney disease in apparently healthy middle-aged and
387 geriatric cats. In: Boehringer Ingelheim: International Renal and Renovascular Symposium.
388 2015. p. 50.

389 31. Paepe D, Verjans G, Duchateau L, Piron K, Ghys L, Daminet S. Routine health screening:

findings in apparently healthy middle-aged and old cats. J Feline Med Surg [Internet]. 2013;15(1):8–19. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23254237

32. O'Neill DG, Church DB, McGreevy PD, Thomson PC, Brodbelt DC. Approaches to canine health surveillance. Canine Genet Epidemiol [Internet]. 2014;1(1):2. Available from: http://www.cgejournal.org/content/1/1/2

33. Venom Coding Group. Veterninary Nomenclature [Internet]. 2016 [cited 2016 Oct 31]. Available from: http://www.venomcoding.org/VeNom/Welcome.html

34. O'Neill DG, Elliott J, Church DB, McGreevy PD, Thomson PC, Brodbelt DC. Chronic kidney disease in dogs in UK veterinary practices: prevalence, risk factors, and survival. J Vet Intern Med [Internet]. 2013;27(4):814–21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23647231

35. Pearce N. Classification of epidemiological study designs. Int J Epidemiol [Internet]. 2012 Apr [cited 2016 Nov 30];41(2):393–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22493323

36. Wakeling J, Moore K, Elliott J, Syme H. Diagnosis of hyperthyroidism in cats with mild chronic kidney disease. J Small Anim Pract [Internet]. 2008 Jun [cited 2016 Aug 23];49(6):287–94. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18422499

37. Centers for Disease Control and Prevention. Epi Info V 7.1.4.0 [Internet]. 2014. Available from: http://wwwn.cdc.gov/epiinfo/7/

38. International Cat Care. Cat Breeds [Internet]. 2015 [cited 2016 Aug 1]. Available from: http://icatcare.org/advice/cat-breeds

39. IRIS. International Renal Interest Society [Internet]. 2015 [cited 2015 Oct 26]. Available from: http://www.iris-kidney.com/

40. Birnbaum ZW, Sirken MG. Design of Sample Surveys to Estimate the Prevalence of Rare Diseases : Three Unbiased Estimates. Washington, D.C; 1965.

41. Hosmer DW, Lemeshow S. Applied Logistic Regression. 2nd ed. Hoboken, New Jersey: John Wiley & Sons, Inc; 2000.

42. Dohoo IR. Veterinary Epidemiologic Research. 2nd ed. Charlottetown, Canada: VER Inc; 2010.

43. Ross SJ, Osborne C a, Kirk C a, Lowry SR, Koehler L a, Polzin DJ. Clinical evaluation of dietary modification for treatment of spontaneous chronic kidney disease in cats. J Am Vet Med Assoc [Internet]. 2006;229(6):949–57. Available from: papers2://publication/uuid/A785DF61-4AAA-43F9-83CA-4E2ED2E2D058

44. Higgs P, Murray JK, Hibbert A. Medical management and monitoring of the hyperthyroid cat: a survey of UK general practitioners. J Feline Med Surg [Internet]. 2014;16(10):788–95. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24423813

45. Brown SA. Mangement of chronic kidney disease. In: Elliott J, Grauer GF, editors. BSAVA manual of canine and feline nephrology and urology. 2nd ed. Gloucester, UK: British Small Animal Veterianry Association; 2009. p. 223–30.

46. Bijsmans ES, Jepson RE, Chang YM, Syme HM, Elliott J. Changes in Systolic Blood Pressure over Time in Healthy Cats and Cats with Chronic Kidney Disease. J Vet Intern Med [Internet]. 2015 May;29(3):855–61. Available from: http://doi.wiley.com/10.1111/jvim.12600

47. Brown S, Atkins C, Bagley R, Carr A, Cowgill L, Davidson M, et al. Guidelines for the Identification, Evaluation, and Management of Systemic Hypertension in Dogs and Cats. J Vet Intern Med [Internet]. 2007 May;21(3):542–58. Available from: http://doi.wiley.com/10.1111/j.1939-1676.2007.tb03005.x

48. Van Hoek I, Daminet S. Interactions between thyroid and kidney function in pathological

conditions of these organ systems: A review. Gen Comp Endocrinol [Internet]. 2009;160(3):205–15. Available from: http://dx.doi.org/10.1016/j.ygcen.2008.12.008

49. Khan TM, Khan KNM. Acute kidney injury and chronic kidney disease. Vet Pathol [Internet]. 2015 May 1 [cited 2015 Nov 13];52(3):441–4. Available from: http://vet.sagepub.com/content/52/3/441

50. Papich M. Drugs and the kidneys: Preventing and managing their potential adverse effects. In: Proceedings of the NAVC North American Veterinary Conference [Internet]. Orlando, FLorida: Internation Veterinary Information Service; 2005. p. 857–60. Available from: http://www.ivis.org/proceedings/navc/2005/SAE/357.pdf?LA=1

51. Birchard SJ, Sherding RG, Sherding RG. Chapter 74 – Constipation and Anorectal Diseases. In: Saunders Manual of Small Animal Practice. 2006. p. 831–44.

52. Korman RM, White JD. Feline CKD: Current therapies - what is achievable? J Feline Med Surg [Internet]. 2013;15 Suppl 1(2013):29–44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23999184

53. Mattin M, O'Neill D, Church D, McGreevy PD, Thomson PC, Brodbelt D. An epidemiological study of diabetes mellitus in dogs attending first opinion practice in the UK. Vet Rec [Internet]. 2014 Apr 5;174(14):349–349. Available from: http://veterinaryrecord.bmj.com/cgi/doi/10.1136/vr.101950

458 TABLES AND FIGURES

459 Figure 1: Flow chart showing case and control selection and inclusion in each study.
460 EPR: Electronic Patient Record

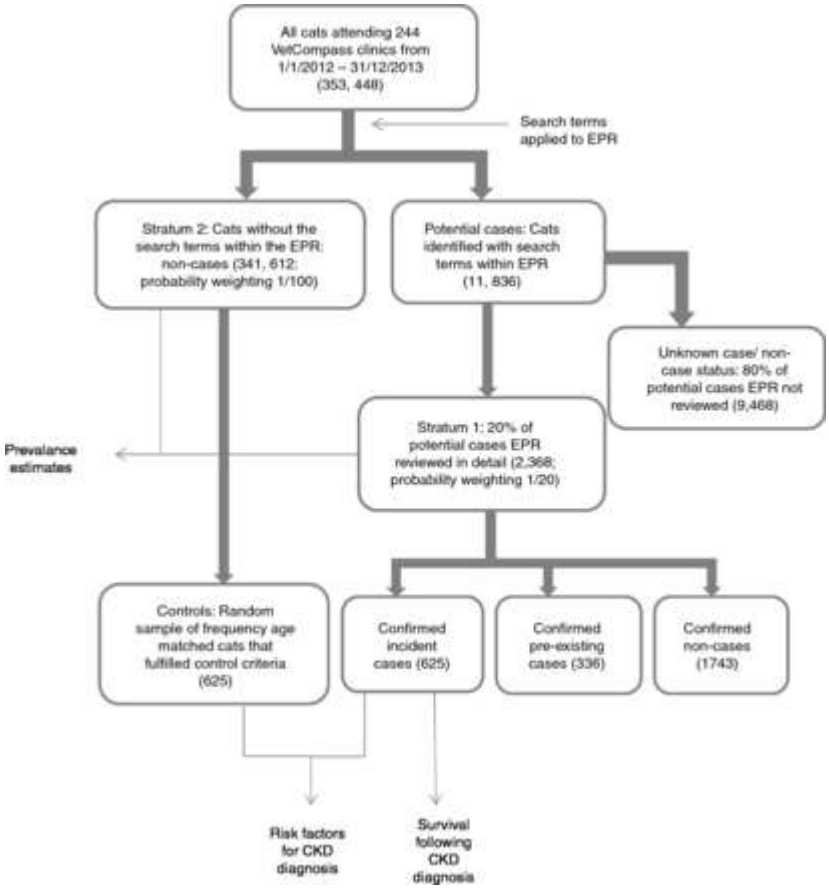

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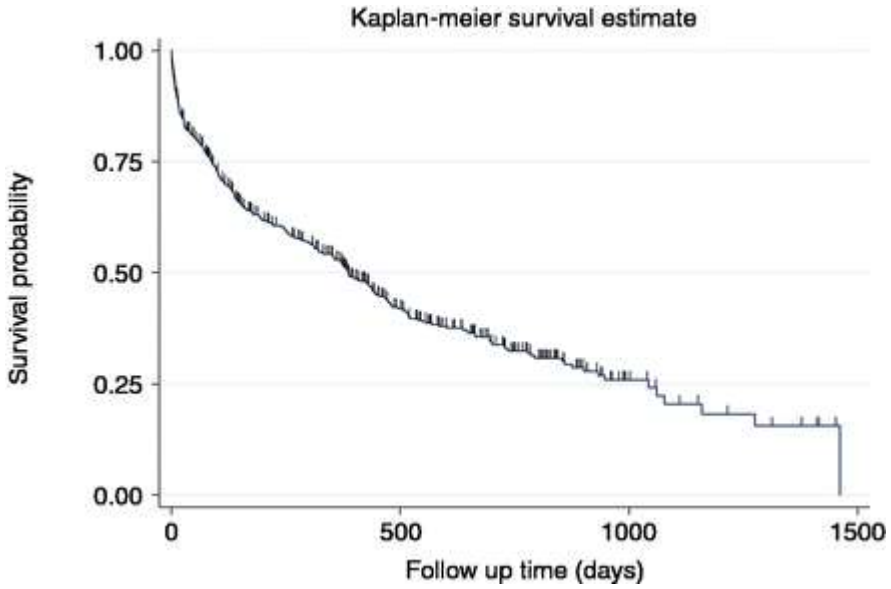
Figure 2: Kaplan-Meier survival curve of all cats diagnosed with CKD in UK primary-care practice from 1/1/2012 – 31/12/2013 with at least 1 day of follow up (n=533)



469 Table 1: Prevalence of chronic kidney disease in cats attending primary-care practice in the UK from

470 1st January 2012 to 31st December 2013

		Denominator	Cases	Prevalence[1]	95% Confidence interval
Overall		353448	961	1.2%	1.1% - 1.3%
Age (years)	0 - < 4.5	118136	17	0.1%	0.02% - 0.07%
	4.5 - < 9	67842	58	0.4%	0.3% - 0.5%
	9 - < 13.5	45597	212	1.9%	1.6% - 2.1%
	13.5 - < 18	30586	478	4.7%	4.3% - 5.1%
	18 - < 22.5	7672	186	6.5%	5.6% - 7.4%
	22.5 - < 27	317	1	1.1%	0% - 3.2%
Breed	Crossbreed	341791	800	1.1%	1.05% - 1.20%
	Burmese	3173	44	5.0%	3.54% - 6.35%
	British Shorthair	7057	14	0.9%	0.42% - 1.33%
	Bengal	4167	3	0.3%	0% - 0.73%
	Persian	4202	25	2.3%	1.44% - 3.24%
	Siamese	2990	22	2.9%	1.72% - 4.08%
	Main Coon	2428	4	0.8%	0.02% - 1.48%
	Other pedigree	11531	38	1.5%	1.00% - 1.92%
	Unknown	3081	11	1.6%	0.66% - 2.51%

471 [1] Calculated using stratified analysis

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Table 2: Treatments prescribed to 549 cats attending primary-care practice in the UK and diagnosed with chronic kidney disease and not euthanased at diagnosis.

Treatment		N (%)
Proprietary renal diet		395 (63.2%)
Antiproteinuric treatment	Benazepril	221 (35.4%)
	Telmisartan	23 (3.7%)
	Ramipril	2 (0.3%)
	Imidapril	1 (0.2%)
Intravenous fluid therapy		121 (19.4%)
Oral Phosphate binder		91 (14.6%)
Amlodipine		66 (10.6%)
Anabolic steroid		61 (9.8%)
Multivitamin injections		61 (9.8%)
Subcutaneous fluid therapy		19 (3.0%)
Potassium supplementation		10 (1.6%)
Anti-nausea medication	H_2 blocker	29 (4.6%)
	Maropitant	20 (3.2%)
	Metoclopramide	4 (0.6%)

Table 3: Multivariable logistic regression analysis for diagnosis of chronic kidney disease in cats attending primary-care practice in the UK from 1st January 2012 to 31st December 2013. Adjusted for vet group effects.

Variable		Case N (%)	Control N (%)	Odds Ratio	95% Confidence Interval	p-value	
						Walds test	Likelihood ratio test
Age	< 9 years	58 (9.3)	89 (9.3)	Reference			0.2
	≥ 9 years	559 (89.4)	559 (89.4)	0.75	0.48 - 1.15	0.18	
Purebred status	Crossbred	530 (84.8)	553(88.5)	Reference			0.03
	Purebred	87 (13.9)	59(9.4)	1.72	1.15 - 2.58	0.008	
	Unknown	8 (1.3)	13(2.1)	1.07	0.38 - 2.93		
Goitre	No	189 (30.2)	33 (5.3)	Reference			0.04
	Yes	61 (9.8)	17(2.7)	0.42	0.21 - 0.85	0.02	
	Not recorded	375 (60.0)	575(92.0)	0.13	0.08 - 0.19		
Heart auscultation abnormal	No	307 (49.1)	266 (45.6)	Reference			0.08
	Yes	113 (18.1)	57 (9.1)	1.64	1.06 - 2.54	0.03	
	Not Recorded	205 (32.8)	302 (48.3)	1.12	0.83 - 1.52		
NSAID[1]	No treatment recorded	389 (62.2)	350 (56.0)	Reference			0.02
	One off treatment recorded	142 (22.7)	182 (29.1)	0.81	0.60 - 1.11	0.19	
	Repeated one off treatment recorded	51 (8.2)	79 (12.6)	0.7	0.44 - 1.10	0.12	
	Long term treatment recorded	43 (6.9)	14 (2.2)	2.34	1.12 - 4.88	0.02	
Hyperthyroidism	No	554 (88.6)	615 (98.4)	Reference			<0.0001
	Yes	71 (11.4)	10 (1.6)	5.7	2.78 - 11.68	<0.001	
Cardiomyopathy	No	612 (97.9)	606 (97.0)	Reference			0.003
	Yes	13 (2.1)	19 (3.0)	0.26	0.10 - 0.65	0.004	
Days since last recorded anaesthetic	0-179 days	40 (6.4)	71 (11.4)	Reference			0.005
	180 - 364 days	20 (3.2)	32 (5.12)	1.21	0.55 - 2.70	0.63	
	No anaesthetic recorded within 1 year	565 (90.4)	522 (83.5)	2.07	1.28 - 3.36	0.003	
Body weight (kg)	0 - 3	51 (8.2)	66 (10.6)	Reference			<0.0001
	3.01 - 3.5	51 (8.2)	58 (9.3)	1.03	0.57 - 1.85	0.92	
	3.51 - 4.05	53 (8.5)	53 (8.5)	0.84	0.46 - 1.54	0.58	
	4.07 - 4.78	82 (13.1)	31 (5.0)	0.36	0.19 - 0.67	0.001	
	4.85 - 9.6	81 (13.0)	22 (3.5)	0.26	0.13 - 0.51	<0.001	
	No weight recorded	307 (49.1)	395 (63.2)	0.7	0.40 - 1.3		

[1]NSAID: Non-steroidal anti-inflammatory drug

497 Table 4: Multivariable Cox proportional hazards model for survival of at least one day following
498 chronic kidney disease diagnosis in 533 cats attending primary-care practice in the UK from 1st
499 January2012 to 31st December 2013 with follow up. Adjusted for vet group effects.

Variable			N	Deaths	Hazard Ratio	95% Confidence Interval	p-value	
							Walds test	Likelihood ratio test
Purebred status		Crossbred	446	261	Reference			0.001
		Purebred	80	40	0.57	0.40 - 0.81	0.002	
		Unknown	7	3	0.3	0.09 - 0.96		
Serum phosphate at diagnosis	0-400 days after diagnosis	<1.5mmol/l	20	4	Reference			<0.0001
		1.5mmol/l +	68	47	5.78	1.91 - 17.32	0.002	
		Not recorded	445	190	4.35	1.49 - 12.71		
	>400 days after diagnosis	<1.5mmol/l	12	7	Reference			
		1.5mmol/l +	11	6	0.47	0.15 - 1.44	0.2	
		Not recorded	159	50	0.45	0.20 - 1.01		
UPC[1]		0-0.2	28	6	Reference			0.01
		0.21-0.4	19	8	3	1.02 - 8.34	0.05	
		>0.4	15	11	4.96	1.78 - 13.81	0.002	
		Not recorded	471	279	2.77	1.21 - 6.35		
Renal diet		No	143	94	Reference			0.0009
		Yes	390	210	0.58	0.45 - 0.75	<0.001	
Phosphate Binder		No	442	257	Reference			0.02
		Yes	91	47	0.68	0.48 - 0.95	0.02	
IVFT[2]		No	419	222	Reference			<0.0001
		Yes	114	82	1.97	1.48 - 2.62	<0.001	
Cystitis		No	440	262	Reference			0.02
		Yes	93	42	0.69	0.49 - 0.97	0.02	
Constipation		Before CKD diagnosis	8	8	Reference			0.01
		At CKD diagnosis	3	2	0.35	0.07 - 1.78	0.2	
		After CKD diagnosis	10	5	0.15	0.05 - 0.50	0.002	
		No constipation	512	289	0.23	0.11 - 0.51	<0.001	
Body weight (kg)		1.65 - 2.78	39	31	Reference			0.0003
		2.8 - 3.23	37	25	0.87	0.50 - 1.51	0.62	
		3.25 - 3.65	45	30	0.54	0.32 - 0.92	0.02	
		3.67 - 4.3	43	29	0.47	0.28 - 0.80	0.005	
		4.3 - 7.5	44	25	0.48	0.27 - 0.83	0.009	
		No weight recorded	325	164	1.4	0.82 - 2.41		

500 [1] Urine protein: creatinine ratio [2]IVFT: Intravenous fluid therapy

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