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Survival analysis of 219 dogs with hyperadrenocorticism attending primary care practice in England

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Abstract

Background Hyperadrenocorticism is an endocrine disease routinely encountered within primary care practice; however, few studies evaluating survival beyond diagnosis have studied this population.

Methods This retrospective cohort study analysed the electronic patient records of 219 cases of hyperadrenocorticism from a sample of dogs attending primary care practices in England. Kaplan-Meier plots examined the cumulative survival and Cox proportional hazard regression modelling identified factors associated with the hazard of all-cause mortality.

Results In the analysis, 179/219 (81.7 per cent) hyperadrenocorticism cases died during the study period with a median survival time from first diagnosis of 510 days (95% CI 412 to 618 days). Trilostane was used in 94.1 per cent of cases and differentiation between pituitary-dependent and adrenal-dependent disease was made in 20.1 per cent of cases. In the multivariable analysis, dogs weighing greater than or equal to 15 kg (HR 1.51, 95% CI 1.06 to 2.15, P=0.023) and those diagnosed greater than or equal to 13 years of age (HR 3.74, 95% CI 2.29 to 6.09, P<0.001) had increased hazards of all-cause mortality. Dogs that had their initial trilostane dose increased had a favourable prognosis (HR 0.49, 95% CI 0.32 to 0.76, P=0.015).

Conclusion This study shows that survival from diagnosis of hyperadrenocorticism appears fair for many dogs and provides primary care practitioners with relatable benchmark prognostic figures.

Introduction

Canine hyperadrenocorticism is an endocrine disease routinely encountered within primary care veterinary practice with an estimated prevalence of 0.28 per cent.[1] The disease is most commonly due to a functional pituitary tumour, although in approximately 15 per cent of cases an adrenal tumour causes the excessive circulatory glucocorticoids which ultimately produce the classical clinical signs in affected dogs.[2 3] Depending on the duration of the disease, these cases show various combinations of polydipsia, polyuria, polyphagia, muscle atrophy, hepatomegaly, lethargy and dermatological changes.[1 4–6] The disease is generally associated with older age, with the average age at diagnosis within primary care practice of nine years.[1] Alongside their older age, the disease often occurs in dogs as one of multiple morbidities including diabetes mellitus (in ~10 per cent of hyperadrenocorticism cases), calcium oxalate urolithiasis, hypothyroidism, pancreatitis and hypertension; however, the causal relationships between these diseases are unproven.[5 7–10] The typical treatment for hyperadrenocorticism in UK dogs is trilostane (Vetoryl Capsules, Dechra Veterinary Products); however, other medical and surgical options are available.

A good understanding of the survival characteristics of dogs with hyperadrenocorticism attending primary care practices is useful for practising veterinary surgeons when informing dog owners. These prognostic indicators play an important role in presenting options for diagnosis as well as treatment, especially given the ongoing expense of treatment and the fact that the disease typically occurs in an older animal where euthanasia may be more frequently considered than disease occurring in younger dogs.[11] Most of the existing survival data have examined dogs undergoing treatment for the disease in a referral setting or outside

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of the UK with studies separating pituitary-dependent disease (PDH) and adrenal-dependent disease (ADH). Median survival times in dogs with PDH treated with trilostane in referral settings have been shown to range from 662 to 900 days.[5 12 13] This is compared to the median survival times of trilostane-treated dogs with ADH which are reported between 353 and 475 days.[4 14] A retrospective study in Japan examined the survival times of 43 dogs with hyperadrenocorticism under primary care and found a statistical difference between dogs treated with trilostane and those not receiving any treatment.[6] Survival times of surgically managed hyperadrenocorticism report 72 per cent–79 per cent survival after 4 years in dogs having undergone hypophysectomy for PDH[15 16] and 533–953 days median survival of ADH cases undergoing adrenalectomy.[17 18] Older age, increased post-adrenocorticotropic hormone (ACTH) cortisol concentrations and increased bodyweight have all been associated with a poorer prognosis for dogs with hyperadrenocorticism.[5 13 14]

The aim of this study was to examine veterinary clinical records to assess the survival characteristics of dogs diagnosed with hyperadrenocorticism under primary care in England. The hypotheses for this study were that age, weight and post-ACTH cortisol concentrations are associated with survival. It was further hypothesised that trilostane treatment favoured survival compared with those that did not receive treatment.

Materials and methods

A retrospective cohort design was used to examine the risk factors for all-cause mortality in the study population. The study used routinely recorded primary care clinical data collected within the Veterinary Companion Animal Surveillance System project, VetCompass[19] and included all dogs under veterinary care at collaborating practices in England between January 1, 2009 and December 31, 2013. The end of follow-up for the study was Aprril 4, 2018. Available clinical data for the study included the attending veterinary surgeons' clinical notes, laboratory results and prescribed treatments recorded within the anonymised electronic patient records (EPRs). The case definition for incident cases of hyperadrenocorticism required the dog to have one of the following: i) a definitive diagnosis of hyperadrenocorticism recorded in the clinical notes; ii) at least one recorded prescription of trilostane, with at least one commonly used screening test for hyperadrenocorticism recorded (ACTH stimulation test, low-dose dexamethasone suppression test (LDDST) or urine cortisol-creatinine ratio (UCCR)). Cases reported as iatrogenic within the EPR were excluded from analysis. The search protocol used to find hyperadrenocorticism cases involved searching the EPR of all study dogs using key search terms (eg, cushin*, hyperadreno*, hac) to identify candidate cases with a higher probability of hyperadrenocorticism. The full clinical records of a random sample of 52 per cent of these candidate cases were manually checked to evaluate against the hyperadrenocorticism case definition and the study inclusion criteria.

Available demographic data for all study dogs included age, sex, neuter status, insurance status, breed, maximum recorded bodyweight and clinic ID. Continuous variables were assessed for linearity with the outcome; where the associations were non-linear, the continuous variables were categorised for analysis. Age at diagnosis (years) was calculated by using their date of birth and date the attending veterinary surgeon diagnosed hyperadrenocorticism. This was categorised into three groups, based around the median age of the study population: less than 10, 10 to less than 13 and greater than or equal to 13 (years). Insurance status was as recorded in the EPRs as 'insured', 'uninsured' or 'unknown' in those with missing information. Individual breeds were included in the analysis if there were greater than or equal to 12 hyperadrenocorticism case dogs of that breed. All other breeds were grouped as 'purebred other'. Maximum recorded bodyweight was split into two groups based around the median weight of dogs within the study population: those less than 15 kg and those greater than or equal to 15 kg. The variable of 'weight compared with breed average' was calculated by comparing the dog's maximum recorded weight with the corresponding breed average.[1]

Additional risk factors and data were extracted manually: date of first diagnosis, date of censorship or death, treatment data reported, recorded comorbidities and diagnostic ACTH blood results. The date of first diagnosis and inclusion into the study was defined as either the first date for a recorded final diagnosis or the first date that trilostane was prescribed for cases without a formally recorded diagnostic term in the clinical notes. The end date was recorded as the date of death or date of the last clinical record during the study period in those that were censored (those still alive at the end of the study period or lost to follow-up). Trilostane dose (mg/kg/day) was recorded from the clinical notes or manually calculated using the prescribed amount (mg) given to the dogs and the nearest recorded weight (kg) to the date of treatment. Trilostane dose was calculated each time a change to the dose was made by the attending veterinarian permitting calculation of the dogs' mean lifetime trilostane dose weighted by the length of time spent on each dose ((dose 1×x days+dose 2×y days+....)/total number of days). A binary variable grouped those with a mean lifetime trilostane dose less than or equal to 3 mg/kg/day and those greater than 3 mg/kg/day. This cut off was based on the recommended starting doses for trilostane in dogs during the study period.[20] Further information on trilostane was extracted including frequency of dose administration and whether changes were made to the initial dose (increased, decreased, stopped or no change

made). A comorbidity was recorded if the dog had another chronic disease, as diagnosed in the EPR (either before or subsequently hyperadrenocorticism) or there was evidence of treatment or management of a chronic disease concurrently with hyperadrenocorticism.[21] This included chronic heart disease, diabetes mellitus, hypertension, hypothyroidism, chronic kidney disease, chronic hepatitis, chronic skin disease (atopy or chronic pyoderma), urolithiasis, malignant neoplastic disease and osteoarthritis. Concurrent diabetes mellitus and hypertension were analysed as separate risk factors.[10 22] Hypertension was defined as those with a conscious systolic arterial blood pressure measurement recorded at greater than 150 mmHg or a diagnosis recorded in the free text.[23] Dogs with neurological signs were defined as those with one or more of the following: seizures with no attributed alternative diagnosis, behaviour change, signs of cognitive dysfunction or apparent blindness.[24 25]

Data were cleaned in Microsoft Excel (Microsoft, Redmond, Washington, USA) before being uploaded into Stata V.15 (StataCorp, College Station, Texas, USA) for statistical analysis. Categorical data were presented showing the count and corresponding percentage. Quantitative data were assessed graphically for normality with normally distributed data summarised using the mean (sd) and non-normally distributed data using the median (IQR and range). Chi-squared analysis compared the association between two categorical risk factors. A Kaplan-Meier plot described the all-cause mortality trend of the case dogs and survival differences were explored using the log-rank test. Median survival time was defined as the point at which the cumulative percentage of dogs surviving from the date of hyperadrenocorticism diagnosis reached 50 per cent.[26] Univariable and multivariable Cox proportional hazard modelling were used to assess associations between the recorded risk factors and hazard of death (all-cause mortality). Risk factors in the univariable analysis with a likelihood ratio test (LRT) of P<0.2 for the outcome of dying were carried forward for multivariable modelling. A forwards stepwise manual approach was used to build the multivariable model with risk factors kept in the final model after assessing for effects of confounding and if they were associated with the outcome of dying (LRT P<0.05). The proportional hazards assumption that the HRs are constant over time was assessed by visual inspection of log-minus-log survival plots and by statistical assessment of Schoenfeld residuals.[27] The clinic ID was assessed as a frailty term to account for the correlated nature of the data across different veterinary practices with the LRT of theta used to assess if within-patient correlation affected the model. Age was assessed for linearity using the LRT for extralinear effect and goodness of fit of the final model was evaluated using visual inspection of Cox-Snell residuals.[26] Confounding factors were assessed by substantial variation in HRs with inclusion of an additional risk factor. Plausible pairwise interactions were examined with the LRT of homogeneity. Dogs with missing data for the risk factors of interest were excluded from the multivariable Cox proportional hazards models. Missing data were also excluded from the univariable analysis if the missing category was the sole reason for a significant risk factor variable (P<0.2).

Sample size calculations using Stata V.15 estimated that for a Cox proportional hazards analysis 208 dogs would be required to observe an HR of 2 at 5 per cent significance, 80 per cent power, with an expected proportion of deaths at 80 per cent and 15 per cent lost to follow-up.

Results

Descriptive statistics

The study included 193,814 dogs attending 110 primary care veterinary practices in England between January 1, 2009 and December 31, 2013. Of the 2502 dogs identified as candidate hyperadrenocorticism cases from the search terms, 1178 (52.0 per cent) were manually reviewed in detail against the case definition. From these candidate cases 219 dogs were included in the analysis. There were 179 (81.7 per cent) cases that died within the study period with 136 (76.0 per cent) of these recorded to be via euthanasia. The remaining 34 (15.5 per cent) dogs were censored and 6 were still alive at the end of the study observation. Median follow-up time for cases was 424 days (IQR 119–779 days, range 1–2192 days).

The maximum recorded bodyweight (kg) of the cases was heavily right skewed with a median of 12.75 kg (IQR 9.20–21.00, range 2.48–65.90). The age at diagnosis (years) was normally distributed with a mean age of 10.99 years (sd 2.49) and a range of 4.46–18.00 years. The cases included 104 females and 115 males of which 86 (82.7 per cent) and 83 (72.2 per cent) were recorded as neutered, respectively. The most represented breed-types were crossbreeds (n=47, 21.5 per cent), Jack Russell terriers (21, 9.6 per cent), Yorkshire terriers (16, 7.3 per cent), Bichon Frise (13, 5.9 per cent), Staffordshire bull terriers (13, 5.9 per cent) and West Highland white terriers (12, 5.5 per cent). Insurance status was unrecorded in 41 dogs with 126 (57.5 per cent) known to be insured. The proportion insured increased to 70.2 per cent in those weighing greater than or equal to 15 kg (chi-squared test, P=0.01). Overall, 206 (94.1 per cent) of the cases received trilostane at some point within their clinical history, 1 dog (0.5 per cent) had surgical treatment via unilateral adrenalectomy and the remaining 12 dogs never received any treatment. Of the dogs initially treated with trilostane, 32 (15.5 per cent) later had their treatment ceased. The starting dose of trilostane was available for 199 (96.6 per cent) cases and was normally distributed around the manufacturer's recommended starting doses with a mean of 3.30 mg/kg/day (sd 1.28).[20] The

mean lifetime trilostane dose was skewed to the right with a median dose of 3.09 mg/kg/day (IQR 2.45–4.50). Frequency of dosing was available for 194 (94.2 per cent) cases with 178 (91.8 per cent) receiving once-daily dosing of trilostane for the duration of their treatment. Of the 100 (48.5 per cent) cases with blood test results recorded at each monitoring ACTH stimulation test, 32 dogs never had a post-ACTH cortisol drop below the upper reference range of 250 nmol/l and 21 had results fall below the lower reference range 40 nmol/l at least once.[28 29] There were 28 dogs with suspected iatrogenic hypoadrenocorticism or adverse response to trilostane at some point in their EPR that were managed by either reducing the trilostane dose or stopping treatment. The most commonly used diagnostic screening tests reported to have been used were the ACTH stimulation test (n=206, 94.1 per cent), LDDST (70, 32.0 per cent) and UCCR (58, 26.5 per cent). All dogs had at least an ACTH stimulation test or an LDDST recorded before diagnosis. Hyperadrenocorticism was differentiated in 44 (20.1 per cent) cases: 30 (68.2 per cent) had PDH and 14 (31.8 per cent) had ADH. Differentiation was based on reported interpretation of ultrasonographic imaging of the adrenals and interpretation of an LDDST. At least one comorbidity to hyperadrenocorticism was recorded in 141 cases (68.5 per cent). Of these, 61.0 per cent had one other comorbidity and a maximum of five comorbidities. Forty-five cases (11.5 per cent) were recorded with central neurological signs, 22 (10.1 per cent) dogs concurrently had diabetes mellitus and 6 (2.7 per cent) had concurrent hypothyroidism.

Survival analysis

The overall median survival time following diagnosis with hyperadrenocorticism (n=219) was 510 days (95% CI 412 to 618 days) (figure 1). Median survival time for cases treated with trilostane (n=206) was 521 days (95% CI 416 to 634 days) and did not differ statistically from the 18 cases not treated with trilostane (178 days, 95% CI 3 to 1015 days, P=0.590). Median survival time for cases that had trilostane treatment ceased or were untreated was 484 days (95% CI 373 to 689) compared with 517 days in those continuously kept on treatment (95% CI 376 to 637 days, P=0.688). Of the dogs where disease differentiation was recorded by the attending veterinary surgeon, the median survival time of those with ADH was 596 days (n=14, 95% CI 166 to 941) and did not differ statistically from the 30 dogs diagnosed with PDH (700 days, 95% CI 305 to 1125, P=0.31). The cumulative proportion of all cases surviving to one year was 0.60 (95% CI 0.53 to 0.66) with 0.35 (95% CI 0.28 to 0.41) surviving to two years.

Univariable Cox proportional hazards analysis identified loose association (P<0.2) of the following risk factors that were taken forward to the final multivariable model: bodyweight, age, insurance status, neurological signs, changes in trilostane dosage and diagnostic pre-ACTH and post-ACTH cortisol levels (table 1).

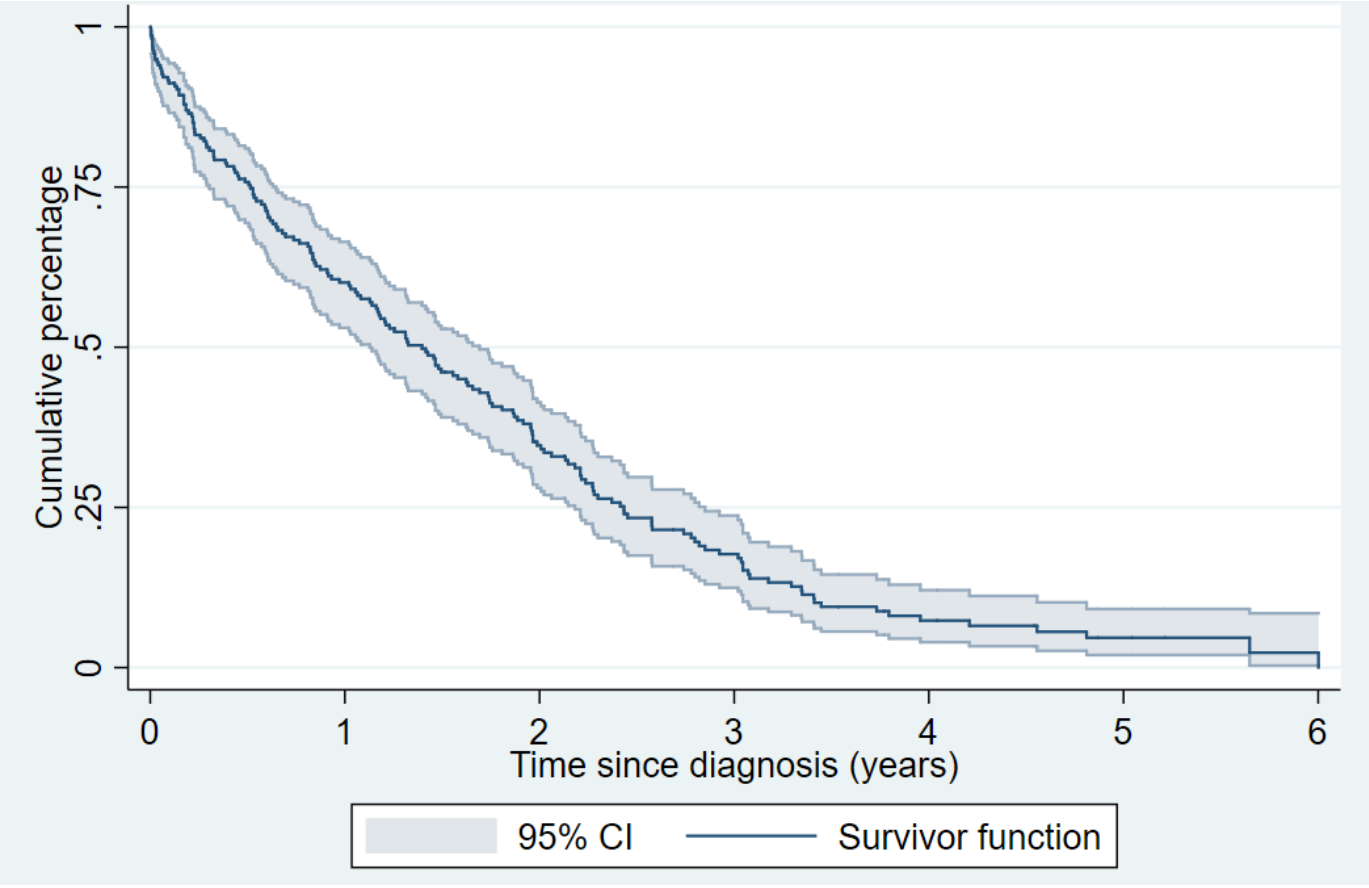

Figure 1 Kaplan-Meier survival curve of all-cause mortality in dogs diagnosed with hyperadrenocorticism at UK primary care practices. Survival time represents the time from when the disease was initially detected until the time of death due to all-cause mortality.

Table 1 Univariable Cox proportional hazards regression analysis for risk factor association with death (all-cause mortality) in dogs diagnosed with hyperadrenocorticism at primary care veterinary practices in England (n=219)

Variable	Frequency (%)	Median survival time (days)	95% CI	HR	95% CI	Category P value*	Variable P value†
Weight (kg)							0.002
<15	135 (61.6)	634	424 to 726	Baseline	-	-	
≥15	84 (38.4)	427	296 to 530	1.61	1.19 to 2.18	0.002	
Age at diagnosis (years)							
<10	74 (33.8)	718	593 to 896	Baseline	-	-	<0.001
10 to <13	96 (43.8)	458	319 to 637	1.48	1.04 to 2.12	0.029	
≥13	49 (22.4)	239	144 to 449	2.94	1.93 to 4.48	<0.001	
Sex neuter							
Female entire	18 (8.2)	427	178 to 1223	1.04	0.56 to 1.92	0.911	0.899
Female neutered	86 (39.3)	442	355 to 637	Baseline	-	-	
Male entire	32 (14.6)	535	159 to 714	1.13	0.73 to 1.76	0.578	
Male neutered	83 (37.9)	546	376 to 718	0.95	0.68 to 1.33	0.780	
Sex							
Female	104 (47.5)	440	355 to 637	Baseline	-	-	0.970
Male	115 (52.5)	535	376 to 683	0.99	0.74 to 1.34	0.970	
Neuter status							
Entire	50 (22.8)	535	220 to 714	Baseline	-	-	
Neutered	169 (77.2)	510	412 to 618	1.13	0.79 to 1.61	0.501	0.506
Insured							
Yes	126 (57.5)	517	412 to 642	0.74	0.52 to 1.07	0.113	0.059
No	52 (23.7)	332	219 to 535	Baseline	-	-	
Unrecorded	41 (18.8)	717	442 to 896	0.55	0.34 to 0.91	0.018	
Breed							
Crossbred	47 (21.5)	432	221 to 726	Baseline	-	-	0.286
Bichon Frise	13 (5.9)	540	119 to 1259	0.72	0.36 to 1.45	0.361	
Jack Russell terrier	21 (9.6)	807	484 to 1445	0.57	0.31 to 1.04	0.065	
Staffordshire bull terrier	13 (5.9)	700	215 to 941	1.01	0.54 to 1.89	0.977	
West Highland white terrier	12 (5.5)	396	72 to 1022	0.93	0.46 to 1.85	0.832	
Yorkshire terrier	16 (7.3)	642	239 to 1015	0.80	0.43 to 1.50	0.487	
Other purebreds	97 (44.3)	440	311 to 568	1.10	0.75 to 1.62	0.618	
Purebred status							
Purebred	172 (78.5)	532	424 to 637	Baseline	-	-	0.637
Crossbred	47 (21.5)	432	221 to 726	1.09	0.77 to 1.55	0.635	
Weight to breed							
Average	81 (37.0)	479	332 to 681	Baseline	-	-	0.900
Above	73 (33.3)	596	441 to 717	0.93	0.65 to 1.33	0.705	
Below	20 (9.1)	373	199 to 739	1.09	0.61 to 1.95	0.769	
Crossbreed	45 (20.6)	389	217 to 726	1.07	0.72 to 1.60	0.728	
Treated with trilostane							
Yes	206 (94.1)	521	416 to 634	Baseline	-	-	0.600
No	13 (5.9)	178	3 to 1015	1.20	0.61 to 2.36	0.590	
Trilostane dose frequency							
Once daily	178 (81.3)	532	424 to 634	Baseline	-	-	0.372
Twice daily	16 (7.3)	833	311 to 1109	0.71	0.41 to 1.23	0.226	
Not given	13 (5.9)	178	3 to 1015	1.20	0.61 to 2.36	0.584	
Unknown	12 (5.5)						
Mean lifetime trilostane dose (mg/kg)							
Not given	13 (5.9)	178	3 to 1015				
≤3	68 (31.1)	449	308 to 605	1.16	0.78 to 1.74	0.462	0.463
>3	131 (59.8)	596	427 to 718	Baseline	-	-	
Missing	7 (3.2)						
Comorbidities							
Neurological signs							
Yes	45 (20.6)	479	300 to 596	1.44	1.01 to 2.03	0.042	0.048
No	174 (79.5)	535	389 to 689	Baseline	-	-	
Hypertensive							
Yes	27 (12.3)	660	429 to 779	Baseline	-	-	0.881
No	15 (6.9)	479	178 to 753	0.93	0.46 to 1.84	0.826	
Not checked	177 (80.8)	479	357 to 605	0.87	0.48 to 1.58	0.650	

Continued

Table 1 Continued

Variable	Frequency (%)	Median survival time (days)	95% CI	HR	95% CI	Category P value*	Variable P value†
Diabetes mellitus							
Yes	22 (10.1)	479	119 to 1102	0.91	0.57 to 1.46	0.698	0.695
No	197 (89.9)	510	412 to 605	Baseline	-	-	
No. of comorbidities							
0	78 (35.6)	334	225 to 432	Baseline	-	-	
≥1	141 (64.4)	568	479 to 715	1.23	0.89 to 1.70	0.198	0.210
Changes to trilostane							
Increased	55 (25.1)	733	532 to 941	0.50	0.34 to 0.73	<0.001	0.002
Decreased	23 (10.5)	681	308 to 830	0.56	0.34 to 0.93	0.023	
No change	94 (42.9)	332	221 to 432	Baseline	-	-	
Stopped	34 (15.6)	546	412 to 717	0.73	0.48 to 1.10	0.133	
Not given	13 (5.9)						
Pre-ACTH cortisol (nmol/l)							
Unknown	154 (70.3)	449	355 to 605	1.44	0.95 to 2.19	0.089	0.154
<150	34 (15.5)	577	340 to 942	Baseline	-	-	
≥150	31 (14.2)	521	84 to 831	1.58	0.93 to 2.70	0.092	
Post-ACTH cortisol (nmol/l)							
Unknown	142 (64.8)	449	334 to 618	1.48	0.98 to 2.23	0.062	0.091
<800	36 (16.5)	779	577 to 1041	Baseline	-	-	
≥800	41 (18.7)	432	269 to 535	1.64	1.00 to 2.68	0.049	

*Wald P value.
†LRT P value.
ACTH, adrenocorticotropic hormone; LRT, likelihood ratio test.

Univariable analysis did not identify associations with any breeds. The origin of the disease and whether or not dogs were treated with trilostane also did not show an association with all-cause mortality in the univariable analysis.

The final multivariable Cox proportional hazards model included three risk factors as well as the clinic ID, included as a frailty term (table 2). Dogs greater than or equal to 15 kg had 1.51 the hazard of dying from all-cause mortality compared with those less than 15 kg (95% CI 1.06 to 2.15, P=0.023). Cases greater than or equal to 13 years of age had 3.74 the hazards of death compared with those less than 10 years (95% CI 2.29 to 6.09, P<0.001). Age was not included as a linear term as this did not improve model fit. Cases that had their starting dose increased had 0.49 the hazards of all-cause mortality compared with those where no dose change was made (95% CI 0.32 to 0.76, P=0.015). No confounding risk factors or interactions were found. Visual interpretation of Cox-Snell residuals showed good model fit and there was no evidence of violation of the proportional hazards assumption.

Table 2 Multivariable Cox proportional hazards regression results for risk factors associated with death (all-cause mortality) among dogs diagnosed with hyperadrenocorticism at primary care veterinary practices in England (n=206)

Variable	HR	95% CI	Variable P value*
Bodyweight (kg)			
<15	Baseline	-	0.023
≥15	1.51	1.06 to 2.15	
Age at diagnosis (years)			
<10	Baseline	-	<0.001
10 to <13	1.70	1.14 to 2.54	
≥13	3.74	2.29 to 6.09	
Changes to trilostane			
No change	Baseline	-	0.015
Increased	0.49	0.32 to 0.76	
Decreased	0.78	0.44 to 1.38	
Stopped	0.72	0.44 to 1.16	
Clinic ID			LRT of theta=0.023

*LRT P value.
LRT, likelihood ratio test.

Discussion

This study identified a median survival time for diagnosed cases of hyperadrenocorticism within primary care practice in England as 510 days (95% CI 412 to 618 days). This estimate lies comfortably within previous survival time estimates ranging from 353 to 900 days.[4–6 12–14] No statistically significant difference in the median survival times of those with ADH (596 days, 95% CI 166 to 941, n=14) and PDH was found (700 days, 95% CI 305 to 1125, P=0.310, n=30). The final multivariable model identified older age at diagnosis, a greater maximum recorded bodyweight and no alteration to the starting trilostane dose as risk factors for increased hazard of death from all-cause mortality. This concurs with previous studies investigating the survival characteristics of dogs with hyperadrenocorticism.[5 6 13 14] The increased hazard with increasing age is unsurprising, with older dogs having a naturally shorter expected onward survival to younger dogs. Dogs weighing greater than or equal to 15 kg had one and a half times the hazard of death from all-cause mortality compared with those less than 15 kg in weight. The variable investigating those with a bodyweight greater than the breed average was

not significant in the univariable analysis therefore this could suggest a breed difference in survival rather than dogs that are overweight. This could be due to a shorter life expectancy in larger breed dogs[30] or that larger breed dogs are thought to be at increased risk of ADH, which in itself has been associated with poorer survival times.[31] The variable looking at changes made to the initial trilostane dose interestingly found that the cases with the initial trilostane dose increased were at reduced risk of dying compared with those with no change made to the initial trilostane dose. The association with this needs to be interpreted cautiously. This effect could be due to reverse causality; cases that live longer may be more likely to have a dose change. It could be that dogs with longer survival may have had more frequent veterinary care with more attention paid to optimise the dosage (either increased, decreased or stopped). Also measurement error of the diagnostic screening tests will have resulted in a number of misclassifications therefore dogs having their trilostane stopped could have been initially incorrectly diagnosed with hyperadrenocorticism. As a higher mean lifetime trilostane dose was not significant in the model, it does not seem that higher doses of trilostane favour survival. The presence of at least one comorbidity did not increase the risk of all-cause mortality in this study. It could have been assumed that the additional burden of a comorbidity may worsen quality of life and add financial pressure therefore influencing euthanasia decisions. The presence of neurological signs was suggestive of increased risk of dying in the univariable results but was not significant after accounting for age in the final model and comorbidity with diabetes mellitus was not associated with reduced survival in this study which contradicts the findings of another study.[8] The proportion of hyperadrenocorticism dogs with concurrent diabetes mellitus has previously been reported at about 10 per cent–14 per cent[5 8] which is consistent with this study, finding 10 per cent of hyperadrenocorticism cases concurrently had diabetes mellitus.

In this analysis, only 44 (21.1 per cent) cases were differentiated into their origin of hyperadrenocorticism with the option to differentiate often suggested by the attending veterinary surgeon but rarely taken up by owners, even though this is deemed an important step in the diagnosis process by the American College of Veterinary Internal Medicine(ACVIM) consensus guidelines.[32] Those cases differentiated were based on interpretation of ultrasonographic imaging of the adrenals or through interpretation of the LDDST with no other methods of differentiation recorded. With the attending veterinarian not always confident in their differentiation and potential measurement error, there is a possibility of misclassification bias of those where an origin of hyperadrenocorticism is recorded. The reason for low uptake of differentiation could be financial, no plans to treat surgically or it was not strongly recommended by the veterinary surgeon. Due to the low numbers of those tentatively differentiated, it was not possible to precisely compare the survival of the two main forms of hyperadrenocorticism in the current study, resulting in low statistical power and wide CIs around the survival estimates. The underlying aetiologies of the two causes of hyperadrenocorticism and their treatment recommendations are quite different yet the overall clinical signs are similar due to the resulting excessive glucocorticoid. They are often grouped together as one disease however in a study such as this, the measure of effect may well be diluted using this approach of a single disease diagnosis.

Median survival for cases treated with trilostane (n=206) was 521 days (95% CI 416 to 634 days) and did not statistically differ from the 18 cases not treated with trilostane (178 days, 95% CI 3 to 1015 days, P=0.590). Due to the low numbers of those untreated resulting in wide CIs and the retrospective design of this observational study, it is not feasible to draw inferences from the comparison of the two treatment groups. A retrospective study in Japan found a significant difference in survival times in those treated with trilostane and those untreated. Interestingly, due to cultural preferences, euthanasia was rarely conducted in Japan reducing some bias that can easily be introduced into observational veterinary studies.[6 33] A future study could be warranted to further investigate the benefits of trilostane treatment.

VetCompass data used in this study are generalisable to veterinary practices in England, with participating practices located across the country using opt-out owner consent.[19] There are limitations to this study. The data analysed were not primarily recorded for research purposes. Cases were included if a diagnosis of hyperadrenocorticism was recorded in the EPR, however no independent confirmation of the diagnosis was possible due to the retrospective nature of the data. Additionally, measurement error from the diagnostic screening tests used could have introduced bias into this study. The recommended gold standard diagnostic screening test is the LDDST, which was recorded in only 32.0 per cent of the dogs included.[32] The ACTH stimulation was the predominant diagnostic test used in this study population which, with a low sensitivity (ie, the proportion of all true cases that are detected), increases the potential for missed cases in primary care practice and consequently in this study.[31 32 34–36] The poor specificity of the UCCR could contribute to misclassification of cases, however this test was always used for diagnosis in combination with an ACTH stimulation or an LDDST for dogs in this study. Therefore, it does not appear that a diagnosis of hyperadrenocorticism was made solely using a UCCR in any of these cases. The outcome of interest was all-cause mortality with the definitive

cause of death rarely recorded therefore it was not possible to attribute whether these deaths were as a result of hyperadrenocorticism. The date of diagnosis recorded in the EPR was used as the starting point for survival estimation, which will differ from the date these cases first developed hyperadrenocorticism. Gaining the definitive diagnosis depends on factors such as the severity of the dog's clinical signs to warrant the initial veterinary consultation or development of concurrent disease associated with hyperadrenocorticism, which raise the clinician's suspicion of the disease.[37] These factors will vary among dogs and likely underestimate the median survival estimate. There is potential for selection bias in this study. Over 95 per cent of dogs in the current study were treated with trilostane at some point, which reflects the management of hyperadrenocorticism within primary care veterinary practice. Confirming a diagnosis of hyperadrenocorticism requires uptake of diagnostic tests and an initial financial outlay by an owner. It is likely that most decisions to diagnose and later differentiate were made by the owner and attending veterinary surgeon before investigation. Therefore, there will be dogs seen at participating veterinary practices with hyperadrenocorticism that were left undiagnosed and hence not included in this study.[37] Another study is warranted to compare the characteristics of dogs suspected of disease and those with a confirmed diagnosis to better understand the reason for not obtaining a definitive diagnosis. In this analysis, 57 per cent of dogs were insured which is a higher proportion than expected.[30] This again corresponds with the above argument that the case definition is more likely to have selected for dogs whose owners wish to and were able to investigate and treat. Finally, an assumption of survival analyses is that the survival pattern of those with complete follow up are the same as those censored; however, in a retrospective study this assumption cannot be assessed. Those lost to follow-up by moving practice or the practice can no longer contact may differ from the treated group.

In summary, this study has highlighted the practicalities of hyperadrenocorticism management within primary care practice in England with disease origin infrequently differentiated and trilostane the predominate treatment for the disease. Survival times following diagnosis were generally fair and are consistent with other studies, with prognosis found to be less favourable in dogs of greater bodyweight, those diagnosed at an older age and those where no changes to the starting trilostane dose were made.

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References

1 O'Neill DG, Scudder C, Faire JM, *et al.* Epidemiology of hyperadrenocorticism among 210,824 dogs attending primary-care veterinary practices in the UK from 2009 to 2014. *J Small Anim Pract* 2016;57:365–73.
2 Feldman EC. Distinguishing dogs with functioning adrenocortical tumors from dogs with pituitary-dependent hyperadrenocorticism. *J Am Vet Med Assoc* 1983;183:195–200.
3 Feldman EC, Nelson RW. Canine and feline endocrinology and reproduction. 4th edn. St Louis, USA: Elsevier Health Sciences, 2014.
4 Helm JR, McLauchlan G, Boden LA, *et al.* A comparison of factors that influence survival in dogs with adrenal-dependent hyperadrenocorticism treated with mitotane or trilostane. *J Vet Intern Med* 2011;25:251–60.
5 Fracassi F, Corradini S, Floriano D, *et al.* Prognostic factors for survival in dogs with pituitary-dependent hypercortisolism treated with trilostane. *Vet Rec* 2015;176:49.
6 Nagata N, Kojima K, Yuki M. Comparison of survival times for dogs with pituitary-dependent Hyperadrenocorticism in a primary-care Hospital: treated with trilostane versus untreated. *J Vet Intern Med* 2017;31:22–8.
7 Ramsey IK, Tebb A, Harris E, *et al.* Hyperparathyroidism in dogs with hyperadrenocorticism. *J Small Anim Pract* 2005;46:531–6.
8 Miceli DD, Pignataro OP, Castillo VA. Concurrent hyperadrenocorticism and diabetes mellitus in dogs. *Res Vet Sci* 2017;115:425–31.
9 Cook AK, Breitschwerdt EB, Levine JF, *et al.* Risk factors associated with acute pancreatitis in dogs: 101 cases (1985-1990). *J Am Vet Med Assoc* 1993;203:673–9.
10 Hess RS, Saunders HM, Van Winkle TJ, *et al.* Concurrent disorders in dogs with diabetes mellitus: 221 cases (1993-1998). *J Am Vet Med Assoc* 2000;217:1166–73.
11 Niessen SJM, Hazuchova K, Powney SL, *et al.* The big PET diabetes survey: perceived frequency and triggers for euthanasia. *Vet Sci* 2017;4. doi:10.3390/vetsci4020027. [Epub ahead of print: 14 May 2017].
12 Barker EN, Campbell S, Tebb AJ, *et al.* A comparison of the survival times of dogs treated with mitotane or trilostane for pituitary-dependent hyperadrenocorticism. *J Vet Intern Med* 2005;19:810–5.
13 Clemente M, De Andrés PJ, Arenas C, *et al.* Comparison of non-selective adrenocorticolysis with mitotane or trilostane for the treatment of dogs with pituitary-dependent hyperadrenocorticism. *Vet Rec* 2007;161:805–9.
14 Arenas C, Melián C, Pérez-Alenza MD. Long-Term survival of dogs with adrenal-dependent hyperadrenocorticism: a comparison between mitotane and twice daily trilostane treatment. *J Vet Intern Med* 2014;28:473–80.
15 van Rijn SJ, Galac S, Tryfonidou MA, *et al.* The influence of pituitary size on outcome after transsphenoidal hypophysectomy in a large cohort of dogs with pituitary-dependent hypercortisolism. *J Vet Intern Med* 2016;30:989–95.
16 Hanson JM, Teske E, Voorhout G, *et al.* Prognostic factors for outcome after transsphenoidal hypophysectomy in dogs with pituitary-dependent hyperadrenocorticism. *J Neurosurg* 2007;107:830–40.
17 van Sluijs FJ, Sjollema BE, Voorhout G, *et al.* Results of adrenalectomy in 36 dogs with hyperadrenocorticism caused by adreno-cortical tumour. *Vet Q* 1995;17:113–6.
18 Massari F, Nicoli S, Romanelli G, *et al.* Adrenalectomy in dogs with adrenal gland tumors: 52 cases (2002-2008). *J Am Vet Med Assoc* 2011;239:216–21.
19 VETCOMPASS. Veterinary companion animal surveillance system, 2018. Available: https://www.rvc.ac.uk/vetcompass [Accessed 4 April 2018].
20 NOAH Compendium. Vetoryl® hard capsules for dogs: clinical Particulars. Available: http://www.noahcompendium.co.uk/?id=-4504342018 [Accessed 6 June 2018].
21 Ording AG, Sørensen HT. Concepts of comorbidities, multiple morbidities, complications, and their clinical epidemiologic analogs. *Clin Epidemiol* 2013;5:199–203.
22 Ortega TM, Feldman EC, Nelson RW, *et al.* Systemic arterial blood pressure and urine protein/creatinine ratio in dogs with hyperadrenocorticism. *J Am Vet Med Assoc* 1996;209:1724–9.

23 Brown S, Atkins C, Bagley R, *et al*. Guidelines for the identification, evaluation, and management of systemic hypertension in dogs and cats. *J Vet Intern Med* 2007;21:542–58.

24 Kent MS, Bommarito D, Feldman E, *et al*. Survival, neurologic response, and prognostic factors in dogs with pituitary masses treated with radiation therapy and untreated dogs. *J Vet Intern Med* 2007;21:1027–33.

25 Bagley RS, Gavin PR, Moore MP, *et al*. Clinical signs associated with brain tumors in dogs: 97 cases (1992-1997). *J Am Vet Med Assoc* 1999;215:818–9.

26 Dohoo IR, Martin W, Stryhn H. Veterinary epidemiologic research. Charlottetown, Canada: AVC Incorporated, 2003.

27 Katz MH. Multivariable analysis: a practical guide for clinicians and public health researchers. Cambridge, UK: Cambridge University Press, 2011.

28 Macfarlane L, Parkin T, Ramsey I. Pre-trilostane and three-hour post-trilostane cortisol to monitor trilostane therapy in dogs. *Vet Rec* 2016;179.

29 Midence JN, Drobatz KJ, Hess RS. Cortisol concentrations in Well-Regulated dogs with Hyperadrenocorticism treated with trilostane. *J Vet Intern Med* 2015;29:1529–33.

30 O'Neill DG, Church DB, McGreevy PD, *et al*. Longevity and mortality of owned dogs in England. *Vet J* 2013;198:638–43.

31 Reusch CE, Feldman EC. Canine hyperadrenocorticism due to adrenocortical neoplasia. pretreatment evaluation of 41 dogs. *J Vet Intern Med* 1991;5:3–10.

32 Behrend EN, Kooistra HS, Nelson R, *et al*. Diagnosis of spontaneous canine hyperadrenocorticism: 2012 ACVIM consensus statement (small animal). *J Vet Intern Med* 2013;27:1292–304.

33 Sugita H, Irimajiri M. A Survey of Veterinarians' Attitudes toward Euthanasia of Companion Animals in Japan. *Anthrozoös* 2016;29:297–310.

34 Feldman EC. Comparison of ACTH response and dexamethasone suppression as screening tests in canine hyperadrenocorticism. *J Am Vet Med Assoc* 1983;182:506–10.

35 Van Liew CH, Greco DS, Salman MD. Comparison of results of adrenocorticotropic hormone stimulation and low-dose dexamethasone suppression tests with necropsy findings in dogs: 81 cases (1985-1995). *J Am Vet Med Assoc* 1997;211:322–5.

36 Monroe WE, Panciera DL, Zimmerman KL. Concentrations of noncortisol adrenal steroids in response to ACTH in dogs with adrenal-dependent hyperadrenocorticism, pituitary-dependent hyperadrenocorticism, and nonadrenal illness. *J Vet Intern Med* 2012;26:945–52.

37 Agniel D, Kohane IS, Weber GM. Biases in electronic health record data due to processes within the healthcare system: retrospective observational study. *BMJ* 2018;361.