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.
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. This is compared to the median survival times of trilostane-treated dogs with ADH which are reported between 353 and 475 days. 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. Survival times of surgically managed hyperadrenocorticism report 72 per cent—79 per cent survival after 4 years in dogs having undergone hypophysectomy for PDH and 533–953 days median survival of ADH cases undergoing adrenalectomy. Older age, increased post-adrenocorticotropic hormone (ACTH) cortisol concentrations and increased bodyweight have all been associated with a poorer prognosis for dogs with hyperadrenocorticism.

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 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 April 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 hyperadrenocorticase 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.

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. 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).

![Kaplan-Meier survival curve](image-url)
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)                     |               |                             |                 |       |         |                   |                   |
| <15                             | 135 (61.6)    | 634                         | 424 to 726      | Baseline | -       | -                 | 0.002             |
| ≥15                             | 84 (38.4)     | 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)     | 444                         | 296 to 530      | 1.61  | 1.19 to 2.18 | 0.002             |
| Sex neuter                      |               |                             |                 |       |         |                   |                   |
| Female entire                   | 18 (8.2)      | 427                         | 178 to 1223     | 1.04  | 0.56 to 1.92 | 0.911             |
| Female neutered                 | 86 (39.3)     | 442                         | 355 to 637      | Baseline | -       | -                 | 0.899             |
| 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)    | 412 to 618                  | 1.13            | 0.79 to 1.61 | 0.501 |
| Insured                          |               |                             |                 |       |         |                   |                   |
| Yes                              | 126 (57.5)    | 517                         | 412 to 642      | 0.74  | 0.52 to 1.07 | 0.113             |
| No                               | 52 (23.7)     | 332                         | 219 to 535      | Baseline | -       | -                 | 0.059             |
| 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)      | 176                         | 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)      | 176                         | 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)      | 176                         | 3 to 1015       |       |         |                   |                   |
| ≤3                              | 68 (31.1)     | 449                         | 308 to 609      | 1.16  | 0.78 to 1.74 | 0.462             |
| >3                              | 131 (59.8)    | 596                         | 427 to 718      | Baseline | -       | -                 | 0.463             |
| Missing                          | 7 (3.2)       |                             |                 |       |         |                   |                   |
| Comorbidities                    |               |                             |                 |       |         |                   |                   |
| Neurological signs               |               |                             |                 |       |         |                   |                   |
| Yes                              | 45 (20.6)     | 479                         | 300 to 596      | 1.44  | 1.01 to 2.03 | 0.042             |
| No                               | 174 (79.5)    | 535                         | 389 to 689      | Baseline | -       | -                 | 0.048             |
| 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
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.

### Discussion
This study identified a median survival time for diagnosed cases of hyperadrenocorticism within primary care veterinary practices 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. 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. 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 or that larger breed dogs are thought to be at increased risk of ADH, which in itself has been associated with poorer survival times. 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. The proportion of hyperadrenocorticism dogs with concurrent diabetes mellitus has previously been reported at about 10 per cent–14 per cent 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. 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. 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. 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. 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. 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. 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. Another study was 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 be less favourable in dogs of greater bodyweight, those consistent with other studies, with prognosis found to times following diagnosis were generally fair and are concluded from the treated group. Finally, an assumption of survival analyses is that the study this assumption cannot be assessed. Those lost 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 predominant 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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