Clinical findings, treatment and outcomes in cats with spontaneous hypoadrenocorticism: 41 cases

Background

Feline hypoadrenocorticism is sparsely reported and nearly all reports comprise of cats with hyponatremia and/or hyperkalemia.

Hypothesis/Objectives

To describe the clinical findings, treatment response and outcome in a population of cats diagnosed with hypoadrenocorticism, including cats with and without hyponatremia and/or hyperkalemia.

Animals

Forty-one cats with hypoadrenocorticism; 36 with and 5 without hyponatremia and/or hyperkalemia.

Methods

Multi-center retrospective observational study. Data for the whole cohort was assessed using descriptive statistics and differences between cats with and without hyponatremia and/or hyperkalemia evaluated.

Results

Median age was 5.7 years (range, 0.2 to 13.8). Twenty-three (56%) cats were male and 18 (44%) were female. Cats with hyponatremia and/or hyperkalemia, were less likely to have a history of vomiting (p=0.006) but more likely to be hypothermic (p=0.034), dehydrated (p=0.043) and/or weak (p=0.043) on examination, compared to cats without hyponatremia and/or hyperkalemia. Prevalence of hypercalcemia was 31.7%. Exocrine pancreatic insufficiency (EPI) was diagnosed in 4/7 cases where tested; all four cats had concurrent cobalamin deficiency. Thirty-five (85.4%) cats survived to discharge. In two cats, hypoadrenocorticism occurred secondary to lymphoma. Median survival time (MST) for all-cause mortality was 2035 days (95% CI 294 – 4380 days); MST for disease-specific mortality wasn't reached.

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Conclusions and clinical importance

One-third of cats with hypoadrenocorticism had hypercalcemia. In some cases, a form without hyponatremia and/or hyperkalemia can be observed. Cats with non-neoplastic associated hypoadrenocorticism that survive initial hospitalization can have a favourable long-term prognosis. Testing for EPI may be warranted in cats diagnosed with hypoadrenocorticism.

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Introduction

Feline hypoadrenocorticism is sparsely reported in the veterinary literature, with most reports limited to one or two cases (1–7). The two largest studies included small case numbers (10 and 11 cats), all of whom had electrolyte abnormalities (hyponatremia and/or hyperkalemia) (4-5). To date, only three cases of cats with non-hyponatremic and non-hyperkalemic hypoadrenocorticism have been reported (8-10).

Even when all reported cases are assessed together, there is limited follow-up information, particularly on survival times. Cats with hypoadrenocorticism have a variable response to treatment; however, long survival times can be reported (4-5).

Larger studies on feline hypoadrenocorticism, including cases both with and without electrolyte abnormalities are warranted to enhance our understanding of this disease in this species.

The primary study aim was to describe the clinical findings of a larger population of cats with hypoadrenocorticism, including both cats with and without electrolyte abnormalities. Our secondary aim was to document response to treatment and outcome in this cohort of cats.

Materials and Methods

Case selection

In this multi-center, retrospective, observational cohort study, cases of feline hypoadrenocorticism diagnosed between 1st January 2000 and 31st December 2021 were recruited. Cases were recruited by advertisement on the European Society of Veterinary Endocrinology and the Society of Comparative Endocrinology list serves, as well as centers being contacted via email. Cases could be included if they'd been diagnosed in primary care practice (PCP) or at a referral center (RC).

Cases were included if they had a post-ACTH serum cortisol of <3 µg/dL (<83 nmol/L) (Supplementary information 1) (11-12). Cats that had received oral, topical (cutaneous/inhalational) or parenterally administered short/intermediate acting steroids, azole antifungal agents or progesterone hormones within four weeks prior to the ACTH stimulation test (ACTHST) were excluded, as were cats that had received long-acting steroids (e.g., methylprednisolone depot) in the previous three months, unless a concurrently increased plasma endogenous ACTH (eACTH) concentration had been documented (13). Additional exclusion criteria included cats that had previously undergone adrenalectomy or hypophysectomy or cats in which the ACTHST was performed to assess adrenal reserve when on treatment for hyperadrenocorticism.

Given the perceived rarity of the condition, cases could be included if they'd been previously published as solitary case reports or small case series.

Data collection

Hospital computerized databases were searched by participating centers to identify cases. Data for each case was entered into an online data-capture platform (CASTOR EDC) and for cases that were referred, both data from the PCP and RC were included. Due to the study design on CASTOR EDC and advertised study requirements, only cases that could be included were entered onto the platform. Data collected from cases included signalment, body weight at diagnosis, country and year of diagnosis, duration of clinical signs (in days) prior to diagnosis, clinical signs reported, clinical findings on examination, clinicopathologic findings (including ACTHST protocols used and results, plasma/serum aldosterone and plasma eACTH measurements), systolic blood pressure results, and results of diagnostic imaging including adrenal gland size/appearance. For cats that had more than one cortisol assessment post-ACTH stimulation, the highest cortisol value obtained was recorded as the post-stimulation result. Cases were categorized as hyponatremic and/or hyperkalemic (HH) if

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hyponatremia and/or hyperkalemia were documented during investigations (either at the PCP and/or RC) or non-hyponatremic and non-hyperkalemic (NHNH) if both hyponatremia and hyperkalemia weren't documented. For all cases, treatment protocols for hypoadrenocorticism were recorded, including in-hospital and post-hospitalization regimes. To assess survival times, cases were followed up until December 2022 via contact with the case veterinarian to ascertain whether for each case, the cat had died, been euthanized (and the cause of this if known), was still alive, or had been lost to follow-up. The last recorded treatment regimen for hypoadrenocorticism was also documented. Clinical control was documented for each case, and defined as resolution of clinical signs, electrolyte disturbances and/or hypoglycemia, if present at diagnosis. Additionally, it was recorded if any case developed further endocrine disease/s post-diagnosis of hypoadrenocorticism and when this occurred. If any cats had undergone cytological and/or histopathological ante- or post-mortem assessment of their adrenal glands and/or their pituitary gland, this information was recorded.

Statistical analysis

Statistical analysis was performed using commercial software (Stata). Descriptive statistics were presented for data from the whole cohort and presented as mean (SD) for parametric continuous data and median and range for non-parametric continuous data; categorical data were presented as the count and corresponding percentage. Due to multiple different laboratories and analyzers being used for blood work assessment, results were classified as being above, within or below the laboratory reference range. Additionally, results of investigations by the PCP and RCs were combined e.g., if hypoglycemia was documented at either the PCP or RC or both the PCP and RC, that cat was classified as having hypoglycemia. For data comparison between cats in groups HH and NHNH, categorical variables were compared with Fisher's Exact test and continuous variables with t-tests for

parametric data and Wilcoxon rank sum test for non-parametric data. Matched pairs of observations were compared using the Wilcoxon matched-pairs signed-rank test. Significance level was set at P <0.05. For assessment of survival, Kaplan-Meier plots were used to describe all-cause mortality and disease-specific mortality for the cohort.

Results

Animals

Forty-one cats were included. Cats came from 14 countries and 24 RCs. Geographical distribution of cases was: Europe (n=32), North America (n=3), Asia (n=3), Australia (n=2) and South America (n=1). Four cats were diagnosed between 2000 to 2010, and the remainder were diagnosed between 2011 and 2021. Forty cats were diagnosed at a RC and one cat was diagnosed in PCP and then referred. On evaluation of sodium and potassium results, 36 (87.8%) cats were classified as HH and five (12.2%) as NHNH. Four cases had been previously published in the literature (10,14-15).

Median age at diagnosis was 5.7 years (range, 0.2 to 13.8). Median bodyweight was 3.8 kg (range, 0.88 to 8.2) in the 40 cases for which this information was available, and median body condition score was 4 out of 9 (range, 1 to 9). Twenty-three (56%) cats were male, with one being entire and 18 (44%) were female, with two being entire. There were no significant differences in these variables between HH cats and NHNH cats (Table 1). The most common breed was the domestic shorthair (n=25), followed by British shorthair (n=4), domestic longhair (n=3), Siamese (n=3), Bengal (n=1), Chartreux (n=1), Maine Coon (n=1), Norwegian Forest (n=1), Ragdoll (n=1) and Tonkinese (n=1).

Clinical signs and physical examination findings

Median duration of clinical signs prior to diagnosis for the whole cohort was 23 days (range, 0 to 365). For group HH it was 21 days (range, 0 to 365) and 50 days (range, 4 to 180) for group NHNH; this difference wasn't statistically significant. Clinical signs reported are

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summarised in table 2 but the commonest signs, occurring in >50% of the cohort included lethargy (87.8%), anorexia/hyporexia (78%), and weakness (61%). Only prevalence of vomiting was significantly different between groups and was higher in group NHNH (p=0.006). Median number of clinical signs reported per cat was 5 (range, 2 to 8).

At time of referral, median heart rate (HR) was 160 beats/minute (range, 60 to 220; n=40), respiratory rate (RR) was 28 breaths/minute (range, 16 to 44; n=34) and rectal temperature (T) was 37.1°C (range, 34.2 to 40°C; n=36). Bradycardia (HR<120 beats/minute), tachypnoea (RR>30 breaths/minute) and hypothermia (T<37.8°C) were noted in 10% (n=4), 29.4% (n=10), and 66.7% (n=24) of cases, respectively. The commonest abnormalities on examination, occurring in >50% of cases included weakness, dehydration, and hypothermia; all three findings were significantly more common in cats in group HH than group NHNH (Table 3). Other examination findings are shown in table 3.

Arterial blood pressure (BP) was assessed in 26 (63.4%) cats. Hypotension (systolic BP<90 mmHg) was documented in 34.6% and hypertension (systolic BP>160 mmHg) in 3.8% of cases.

Routine laboratory findings

Findings on routine complete blood count and biochemistry are summarized in table 4. The most commonly reported abnormalities, occurring in >50% of the cohort (when assessed), included azotemia (increase in urea and/or creatinine), hyponatremia, hyperkalemia, hypochloremia, increased creatine kinase and hyperphosphatemia. The prevalence of hypercalcemia (total and/or ionized) was 31.7%. Ionized calcium was only assessed in cats from group HH and was increased in 8/14 cases [range 5.3 to 8.3 mg/dL (1.33 to 2.07 mmol/L)] in which it was evaluated. No significant differences were documented in the prevalence of clinicopathological abnormalities between the HH and NHNH groups except for hyponatremia and hyperkalemia (as expected from their definition).

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Regarding urine concentration, only 17 cats had a urine sample obtained before fluid therapy and of those, urine specific gravity (USG) ranged from 1.005 to 1.045. Twelve of these cats were azotemic, with USG ranging from 1.016 to 1.045; 50% had a USG <1.035. For non-azotemic cats, USG ranged from 1.005 to 1.038.

Notable further abnormalities were those of cobalamin and feline trypsin-like immunoreactivity (fTLI) results. Serum cobalamin was assessed in 11/41 (26.8%) cats and fTLI in 7/41 (17.1%) cats. Cobalamin deficiency was documented in 5/11 (45.5%) cases (three cats in group HH and two cats in group NHNH) and exocrine pancreatic insufficiency (EPI) in 4/7 (57.1%); all cases had weight loss and/or gastrointestinal tract signs reported (10). All cats with cobalamin deficiency had undergone fTLI assessment and four were diagnosed with concurrent EPI; three of these cats were also suspected to have a chronic enteropathy based on ultrasound findings (diffuse thickening of the muscularis propria +/- submucosa). The remaining cat with cobalamin deficiency was also diagnosed with a suspected chronic enteropathy. None of the five cats had gastro-intestinal tract biopsies performed at the time of hypoadrenocorticism diagnosis.

Testing for hypoadrenocorticism

Testing occurred a median of two days post-referral (range, 0 to 30). Basal cortisol was utilized as an initial screening test in 12 cats and was undetectably low in seven. Timings of cortisol testing post-ACTH stimulation are shown in supplementary information 2. Post-ACTH stimulation cortisol levels were undetectably low in 22 cats; in the remaining 19 cats the median value was 0.9 µg/dL (24.8 nmol/l) (range, 0.1 to 1.8 µg/dL). Aldosterone concentrations were assessed in 11 cases (including two cats from group NHNH), five of which had aldosterone assessed both pre- and post-ACTH stimulation; all 11 cases had aldosterone concentrations below laboratory reference ranges or were undetectably low. Plasma eACTH concentrations were assessed in 13 cats including one in group NHNH. For

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nine cases, the eACTH concentration was recorded as being above the upper limit of detection for the utilised assay [≥600 pg/mL (n=1) and ≥1250 pg/mL (n=8)] and for the other four cases it ranged from 1218 to 1494 pg/mL. Aldosterone and eACTH concentrations, where assessed, were suggestive of those cases being due to primary hypoadrenocorticism. Two cats received glucocorticoid treatment before diagnosis (0.1 mg/kg dexamethasone 28 days prior to the ACTHST and an unknown dose of dexamethasone 21 days prior to the ACTHST) and for three cats, information on previous steroid treatment was unknown; in all five cats, plasma eACTH concentrations were ≥1218 pg/mL.

Imaging

For assessment of imaging findings, only results from RCs were available for review.

Thoracic imaging

Sixteen cats had thoracic imaging performed, with radiographs (n=15), or computed tomography and radiographs (n=1). One case had microcardia documented; megaoesophagus was not reported in any case.

Adrenal gland imaging

Abdominal imaging was performed in 37 cats; 33 had an ultrasound, three had an ultrasound and radiographs, and one had an ultrasound and computed tomography. Adrenal gland sizes, when available, had been measured during ultrasonography using maximal thickness. The right adrenal gland was assessed in 29/37 cats and the left in 31/37 cats. In two cats, lymphoma affecting the adrenal glands was documented on post-mortem. For these cases, one had adrenal widths of 8 mm bilaterally and in the other, the adrenal glands were replaced by a mass measuring 8 x 5 cm. For the remaining cats, the median width of the right adrenal gland was 2.8 mm (range, 1.5 to 6 mm) and in four cases the adrenal gland couldn't be seen. The median width of the left adrenal gland was 3 mm (range, 1.7 to 5.4 mm) but couldn't be seen in three cases. Adrenal gland echogenicity was reported as normal in most cases but

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there were two cases each that had a hyper- and hypoechoic appearance reported and two separate cases had evidence of adrenal gland mineralization.

Treatment of hypoadrenocorticism

In-hospital glucocorticoid/mineralocorticoid treatment consisted of hydrocortisone (n=7), dexamethasone (n=12), methylprednisolone (n=3), desoxycorticosterone pivalate (DOCP) (n=10), prednisolone (n=23), prednisone (n=1) and/or fludrocortisone acetate (FC) (n=19); the majority of cats received a combination of treatments.

Intravenous fluid therapy was administered in 90.2% (n=37) of cases at the RCs. One cat required two packed red blood cell transfusions due to the development of marked anaemia during hospitalisation.

Thirty-five (85.4%) cats survived to discharge, including 4/5 (80%) in group NHNH and 31/36 (86.1%) in group HH. Of the remaining six cats (14.6%), one died due to cardiopulmonary arrest and five were euthanized. Euthanasia reasons included poor response to treatment (n=4) and lymphoma as the cause of hypoadrenocorticism (n=1). For cats that survived to discharge, median hospitalization length post-diagnosis was four days (range, 0-10). For cats that didn't survive to discharge, hospitalization length prior to death/euthanasia ranged from two to thirteen days post-diagnosis.

Initial at home treatment protocols for cats in group HH were: prednisolone and FC (n=15), prednisolone and DOCP (n=9), prednisolone alone (n=2), FC alone (n=3), prednisone and FC (n=1) and methylprednisolone and DOCP (n=1). The four cats in group NHNH were started on prednisolone (n=3) or prednisolone and DOCP (n=1); the latter case had documented hypoaldosteronism. Median starting dose of FC was 0.02 mg/kg/day (range, 0.01-0.14) and in eight cats was divided twice daily. Starting dose for DOCP was 2.2 mg/kg (range, 1.2-3.1) and for prednisolone was 0.5 mg/kg/day (range, 0.2-2.2). When assessing the type of mineralocorticoid replacement prescribed during the study period, 11.8% of cases diagnosed

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before 2016 were started on DOCP compared to 71.4% of cats diagnosed from 2016 onwards.

One HH cat initially started on FC, was changed onto DOCP 10 months post-diagnosis due to an inability to control electrolytes. Another HH cat initially started on prednisolone alone had DOCP treatment added one-month post-diagnosis due to recurrence of hyperkalemia.

Clinical control for cats surviving hospitalization, occurred a median of five days post-diagnosis (range, 1 to 247); two cats didn't stabilize before euthanasia at 10- and 40-days post-diagnosis.

At the end of follow-up, treatment regimens (when known) for HH cats that had survived initial hospitalization were: prednisolone and DOCP (n=9), prednisolone and FC (n=8), FC (n=5), methylprednisolone and DOCP (n=2), prednisone and FC (n=1) and prednisolone (n=1). For cats in group NHNH, treatment regimens were either prednisolone (n=3) or prednisolone and DOCP (n=1). Median final doses of FC were 0.03 mg/kg/day (range, 0.01–0.05) and 0.33 mg/kg/day (range, 0.02–2) for prednisolone. Median final dose for DOCP was 2.2 mg/kg (range, 1.3–3), with four cats requiring a dose escalation, three cats a dose decrease and three cats remaining at the same starting dose; four cats required administration more frequently than every 28-30 days, at 21-25 day intervals. There was only a significant difference between the starting and final dose for prednisolone (p=0.01).

Follow-up

Median follow-up period of the whole cohort was 287 days (range, 0 to 5103). At the end of follow-up for all cases, 12 (29.3%) were still alive, six (14.6%) had died, 14 (34.1%) had been euthanized and nine (22%) had been lost to follow-up. Of the four NHNH cats that survived hospitalization, two were euthanized at 10- and 298-days post-diagnosis, one was lost to follow-up 133 days post-diagnosis and one cat was still alive 395 days post-diagnosis.

No NHNH cats that were administered prednisolone alone were documented to develop

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hyponatremia and/or hyperkalemia during follow-up (median 133 days; range, 10 to 395). Of the 31 HH cats that survived hospitalization, seven were euthanized at a median of 670 days post-diagnosis (range, 30 to 5103), five cats died at a median of 600 days post-diagnosis (range, 9 to 4380), eight cats had been lost to follow-up at a median of 110 days post-diagnosis (range, 4 to 1460) and 11 cats were still alive at a median of 539 days post-diagnosis (range, 280 to 3803).

Of the cases that died or were euthanized during post-hospitalization follow-up, five were attributed to hypoadrenocorticism: aspiration pneumonia suspected secondary to vomiting +/- neurological deterioration (weakness) (n=2), relapse of clinical signs (n=1), cardiac arrest due to the owner not administering medication (n=1), and lymphoid neoplasia as the cause of hypoadrenocorticism (n=1). For the other nine cats, causes weren't directly attributed to hypoadrenocorticism and included gastro-intestinal tract neoplasia (n=2), unknown (n=2) and one each of age, renal disease, toxin ingestion, central nervous system disease and feline infectious peritonitis. Median survival time (MST) for all-cause mortality was 2035 days (95% CI 294 – 4380 days) (Figure 1); however, MST for disease-specific mortality wasn't reached (Figure 2). One-year proportional survival for disease-specific mortality was 0.76 (95% CI 0.59 – 87).

The MSTs for all-cause mortality weren't significantly different between cats treated with DOCP (didn't reach median survival), FC (4380 days; 95% CI 600 – unknown) or prednisolone alone (2035 days; 95% CI 10 – unknown) (the cat treated with FC and then DOCP was omitted from this analysis). For disease-specific mortality for treatment groups, none of the three treatment groups reached median survival preventing statistical comparisons (Figure 3). The difference in median all-cause mortality between cats in group HH and cats in group NHNH wasn't statistically significant and for disease-specific mortality, median survival wasn't reached (Figure 4).

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Development of endocrine disease on follow-up

One cat developed hyperthyroidism 2373 days post-diagnosis, and one cat developed diabetes mellitus 135 days post-diagnosis (10).

Adrenal and/or pituitary gland cytology and histopathology

Post-mortem histopathology of the adrenal glands was performed in seven cats; adrenal gland cytology or assessment of the pituitary gland wasn't performed in any case. In two cases, euthanised at 2- and 30-days post-diagnosis, large-cell lymphoma was documented as the cause of hypoadrenocorticism. In the other five cats, the following findings were documented: bilateral T-cell rich lymphoplasmacytic adrenalitis (n=1), bilateral necrosis of the adrenal cortex not accompanied by inflammation (n=2), and bilateral adrenocortical atrophy and fibrosis (n=2) (10).

Discussion

Our study provides a more comprehensive documentation of the clinical presentation, investigative results, treatment, and outcome of cats diagnosed with hypoadrenocorticism than previously reported in the veterinary literature. Our study results support previous findings including the possibility of a breed predisposition for British shorthaired cats and a higher required starting dose of DOCP compared to dogs. Our study also demonstrated a higher than previously reported prevalence of hypercalcemia, the concurrent presence of EPI and/or cobalamin deficiency in several cases of hypoadrenocorticism and is the first study to include a group of cats with non-hyponatremic and non-hyperkalemic hypoadrenocorticism. It also provides further information on the survival of these cases.

In dogs, certain breeds are at an increased risk of developing hypoadrenocorticism; however, in cats this has been harder to discern due to the limited numbers published in the literature (16–18). An increased prevalence in British shorthairs has been proposed in a recent Swiss study, as 54.5% of the study population (11 cats), were of this breed (4). Additionally, three

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further case reports of British shorthairs with hypoadrenocorticism have been published (1,19-20). In our study population, the percentage of British shorthairs (~10%) wasn't as notable but could still further support the possibility of a breed predisposition to this disease. A reason for the marked difference in prevalence between the two studies could be the varying population sizes and degree of inter-breeding of British shorthairs between countries, as our study included cats from around the world, rather than just one country. However, given this growing evidence-base, breed could help increase the index of suspicion for hypoadrenocorticism (21).

This study has provided findings for five cats without hyponatremia and/or hyperkalemia. Two cats underwent aldosterone testing, with one additionally having eACTH assessment; in both cases, results were supportive of primary hypoadrenocorticism. Only three previous NHNH feline cases have been reported; one had secondary hypoadrenocorticism, one had steroids administered before diagnosis and an eACTH wasn't performed to exclude pituitary suppression secondary to this and the third case was included in our study population (8-10). However, our documentation of four additional NHNH cases provides further evidence that hypoadrenocorticism in cats should be considered as a differential in relevant cases regardless of typical electrolyte changes, as has been shown in dogs (22-24). In contrast to what's been documented in dogs, none of the NHNH cats treated with prednisolone alone developed hyponatremia and/or hyperkalemia on follow-up; however, median follow-up of this group was limited to 133 days (25). In NHNH hypoadrenocorticoid dogs, electrolyte abnormalities can occur in up to 14% of cases, as long as 51 months post-diagnosis (25-26). Based on the number of NHNH cats included and the relatively short median follow-up time, there's not enough data to advise as to whether ongoing electrolyte monitoring is standardly required in cases started only on glucocorticoid supplementation and for how long post-diagnosis this should be performed.

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Few studies have directly compared HH dogs to NHNH dogs within their study population but of those that have, NHNH cases have been documented to be older at diagnosis, have a longer duration of clinical signs, be more likely to have anemia, hypoalbuminemia and hypocholesterolemia and less likely to have hypercalcemia than HH cases (26-27). Similar differences weren't seen in our study, but this may have been due to the small number of NHNH cats included. However, only HH cats were documented to be hypercalcemic. The prevalence of hypercalcemia noted in our study (31.7%), was higher than that previously documented in the feline literature (~10%) but parallels that documented in dogs (4-5,27). A reason for this difference could be that we included both ionized and total calcium results in our data, compared to other studies in which only total calcium was reported. Based on our findings, the presence of hypercalcemia could help heighten the suspicion of hypoadrenocorticism and demonstrates that hypoadrenocorticism should be considered as a differential in hypercalcemic cats (28).

An interesting finding in our study was the documentation of EPI and/or cobalamin deficiency in five cases, including one previously published case (10). In dogs, cobalamin deficiency has been documented to occur in up to 18.2% of NHNH cases and proposed causes of this have included a concurrent enteropathy and/or it being directly linked to hypoadrenocorticism (23). In our study, cobalamin deficiency was documented in both groups. Causes were attributed to concurrent presence of EPI and/or a chronic enteropathy, but a direct consequence of hypoadrenocorticism couldn't be definitively excluded. In humans, there's a link between hypoadrenocorticism and the autoimmune condition pernicious anaemia with the latter occurring secondary to a deficiency/absence of intrinsic factor, which in humans is produced in the stomach, resulting in cobalamin deficiency (29). In contrast, in cats intrinsic factor is exclusively produced by the exocrine pancreas and so diseases affecting the pancreas can result in cobalamin deficiency (30). The cause of EPI in

cats is typically attributed to pancreatitis, which in most cases is presumed to be idiopathic; however, autoimmune causes cannot be excluded. Therefore, there is the possibility that similar to humans, a concurrent autoimmune disease is present, resulting in a lack of intrinsic factor and subsequent cobalamin deficiency in some cats with hypoadrenocorticism (10,31–33). As cobalamin status was only assessed in 26.8% of the population and fTLI in 17.1%, the prevalence of cobalamin deficiency and/or EPI may have been underestimated. Based on our results, testing for EPI in cats diagnosed with hypoadrenocorticism and vice versa warrants future consideration.

Although uncommon in our population, 4.9% of cases were documented to have lymphoid neoplasia as the cause of their hypoadrenocorticism. Ultrasonography in both cases showed a mass replacing the adrenal glands or adrenomegaly. These findings document the importance of performing abdominal imaging as part of the diagnostic work-up in cats with hypoadrenocorticism to screen for lymphoma as a possible cause.

Similar to dogs, historically cats with hyponatremic and/or hyperkalemic hypoadrenocorticism were more commonly treated with FC +/- prednisolone compared to DOCP and prednisolone (5,19,34–37). However, as DOCP has been documented to be more effective in suppressing plasma renin activity than FC, combined with availability of a canine licenced formulation of DOCP in Europe, the majority of dogs diagnosed more recently are treated with DOCP and prednisolone and the same trend has been seen in cats (4,38–40). This trend was echoed in our study with 11.8% of cats diagnosed prior to 2016 being started on DOCP for mineralocorticoid replacement compared to 71.4% of cats diagnosed from 2016 onwards. Despite this trend, there was no statistical difference in MST between cats treated with FC vs DOCP in our study when assessing all-cause mortality; however, this may have been biased by cats treated with DOCP having shorter follow-up times due to when they were diagnosed. Further assessment would require analysis of disease-specific mortality, which

wasn't possible in this study due to MSTs not being reached by the end of the study period, and utilisation of a randomized controlled trial.

Canine studies have documented that lower DOCP starting doses (1.1 and 1.5 mg/kg) than the manufacturers recommendations (2.2 mg/kg) appear to be more appropriate in most cases (39,41-42). However, in contrast, a starting dose of 2.2 mg/kg has been advised in cats as the median end-treatment dose in a study assessing DOCP in cats was 2.3 mg/kg and 4/6 cats started on a dose <2.2 mg/kg required dose escalation (4). Our study findings would further support this as our median final dose was similar at 2.2 mg/kg and all three cats started on doses <2.2 mg/kg required dose escalation.

Our study documented the long-term prognosis of cats with hypoadrenocorticism to be favourable, as has been documented in dogs, with MSTs for all-cause mortality being >5.5 years and MSTs for disease-specific mortality being >10 years (34). However, in-hospital mortality rates at diagnosis were 15%, higher than that documented in dogs, suggestive that cats may be either diagnosed at a later stage of the disease or be more difficult to stabilize (43-45). This difficulty in stabilisation could be due to their higher requirement for mineralocorticoids and glucocorticoids and/or the presence of concurrent disease that was noted in several cats in this study, which may have impacted their response to treatment (4). Increased difficulties to stabilize these patients was further demonstrated by the longer hospitalization times in our cohort, which paralleled that previously reported in the feline literature, compared to that documented for dogs (4,44-45). However, as in-hospital treatment wasn't standardised, treatment as a confounding factor couldn't be excluded. This potential difference between cats and dogs with hypoadrenocorticism should be considered when assessing initial clinical response to treatment following diagnosis.

There were several limitations to our study, with the main ones being its retrospective and multi-center nature. This resulted in multiple laboratories being utilized, preventing

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assessment and comparison between groups of specific laboratory values, a lack of standardized investigations and treatment, missing data and contributed to the number of cases lost to follow-up. This may have influenced some of the study findings, especially the assessment of the number of cats with EPI and cobalamin deficiency and the survival/outcome data.

For our inclusion criteria, we elected to use a higher cut-off for the post-ACTH cortisol levels than previously utilised in feline studies. This was to address the possible variation in cortisol measurements between laboratories and enable cases of partial ACTH deficiency to be identified and included, without additionally including cases with a potential alternative disease as the cause of their signs (11-12,46). This approach could have resulted in some ambiguous cases being included. However, as all cases included had a post-ACTH cortisol level lower than the standardly used cut-off of < 2 µg/dL (<55 nmol/L), this wasn't identified to be a concern.

Even though the study was opened up to centers world-wide (including PCPs and RCs) and a 21-year time period utilized to increase study size, the number of cats included was still relatively small and isn't comparable to case numbers documented in studies on canine hypoadrenocorticism (27,34). This supports the rarity of this condition in cats or potentially demonstrates the fact that this disease is rarely tested for.

Four cats were included that had been previously published as case reports/series. As this number totalled < 10% of the study population, their inclusion strengthened our findings i.e., documentation of EPI in several new cases, alongside the previously reported case that was included, and readers have been made aware of which previously published cases these were, their inclusion should not have negatively impacted on, or led to potential bias of, our findings.

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Cases were classified as NHNH based solely on electrolyte levels, as aldosterone levels weren't assessed in all cases and so some cats may still have been mineralocorticoid deficient; this was unavoidable due to the retrospective study design. Possible mis-categorisation has also been documented as a limitation in previous canine studies as aldosterone hasn't always been measured in retrospective studies, due to laboratory availability of this test and/or associated costs (26-27). The small number of NHNH cats may have confounded our results when assessing for statistical differences with the HH group, therefore findings relating to the comparison of these two groups should be interpreted with caution.

In conclusion, our study identified that cats with hypoadrenocorticism can present with or without hyponatremia and/or hyperkalemia, demonstrating that this condition should be considered in cases presenting with suggestive clinical signs/examination findings regardless of electrolyte values. A higher than previously reported prevalence of hypercalcemia was identified and as such, its presence can help increase the clinical index of suspicion for hypoadrenocorticism. This is the first time a possible link between feline hypoadrenocorticism and EPI has been demonstrated and assessment for cobalamin deficiency and EPI warrant future consideration in cases diagnosed with hypoadrenocorticism. Our study suggests screening for lymphoma as the cause of hypoadrenocorticism is advisable. Cats with non-neoplastic associated hypoadrenocorticism that survive initial hospitalization have a favourable long-term prognosis.

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Variable	All cats (n=41)	HH cats (n=36)	NHNH cats (n=5)
Age in years (median; range)	5.7; 0.2 to 13.8	5.3; 0.2 to 13.8	6.1; 0.4 to 11.2
Weight in kg (median; range) (n=40)	3.82; 0.88 to 8.20	3.80; 0.88 to 8.20	3.95; 2.42 to 6.10
Body condition score (out of 9) (median; range)	4; 1 to 9	4; 1 to 9	4; 2 to 7
Sex (number, percentage; neutered, entire)	Male (23, 56%; 22N, 1E) Female (18, 44%; 16N, 2E)	Male (21, 58%; 20N, 1E) Female (15, 42%; 14N, 1E)	Male (2, 40%; 2N) Female (3, 60%; 2N, 1E)
Breed	DSH (n=25), BSH (n=4), DLH (n=3), Siamese (n=3), and one each of Bengal, Chartreux, Maine Coon, Norwegian Forest, Ragdoll, Tonkinese	DSH (n=22), BSH (n=4), Siamese (n=3), DLH (n=2), and one each of Chartreux, Maine Coon, Norwegian Forest, Ragdoll, Tonkinese	DSH (n=3), DLH (n=1), Bengal (n=1)

Table 1. Descriptive statistics of the signalment of all included cases (all cats), and then further divided into cats classified as hyponatremic and/or hyperkalemic (HH) and cats classified as non-hyponatremic and non-hyperkalemic (NHNH). When the information was

not available for all cases, the total number of cats for which this information was available, is shown in the first column.

Abbreviations: N, neutered; E, entire; BSH, British shorthair; DSH, domestic shorthair; DLH domestic longhair

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Clinical sign	All cats (n=41) (n, %)	HH cats (n=36) (n, %)	NHNH cats (n=5) (n, %)
Lethargy	36; 87.8%	32; 88.9%	4; 80.0%
Anorexia/hyporexia	32; 78.0%	29; 80.6%	3; 60.0%
Weakness	25; 61.0%	24; 66.7%	1; 20.0%
Weight loss	20; 48.8%	18; 50.0%	2; 40.0%
Vomiting	16; 39%	11; 30.6%*	5; 100%* (p = 0.006)
Diarrhoea	11; 26.8%	9; 25.0%	2; 40.0%
Collapse	10; 24.4%	8; 22.2%	2; 40.0%
Nausea	9; 22.0%	8; 22.2%	1; 20.0%
Seizures/tremors	6; 14.6%	6; 16.7%	0; 0%
Hypodipsia	6; 14.6%	5; 13.9%	1; 20.0%
Constipation	4; 9.8%	4; 11.1%	0; 0%
Polydipsia	4; 9.8%	4; 11.1%	0; 0%
Difficulty swallowing	3; 7.3%	3; 8.3%	0; 0%
Polyphagia	2; 4.9%	0; 0%	2; 40.0%
Polyuria	2; 4.9%	2; 5.6%	0; 0%
Weight gain	2; 4.9%	2; 5.6%	0; 0%
Haematochezia	1; 2.4%	0; 0%	1; 20.0%
Other	Smaller than littermate (1; 2.4%), aggression (1;	Aggression (1; 2.8%), sneezing	Smaller than littermate (1; 20.0%)

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	2.4%), sneezing whilst eating (1; 2.4%)	whilst eating (1; 2.8%)	

Table 2. The clinical signs reported in all included cases (all cats), based on assessment of both the clinical history from the PCP and RC (listed from most common to least common) and then further divided into cats classified as hyponatremic and/or hyperkalemic (HH) and cats classified as non-hyponatremic and non-hyperkalemic (NHNH). Data are presented as number and frequency. Significant differences ($p < 0.05$) between the HH and NHNH groups are shown as *.

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Clinical examination finding	**All cats (n=40) (n, %)**	**HH cats (n=35) (n, %)**	**NHNH cats (n=5) (n, %)**
Hypothermia (<37.8°C) (n=36)	24; 66.7%	23; 74.2%*	1; 20.0%* (p = 0.034)
Dehydrated	26; 65.0%	25; 71.4%*	1; 20.0%* (p = 0.0043)
Weakness	26; 65.0%	25; 71.4%*	1; 20.0%* (p = 0.0043)
Tachypnoea (RR>30 bpm) (n=34; NHNH cats = 4)	10; 29.4%	9; 30.0%	1; 25.0%
Neurological abnormalities (four cats had more than one neurological abnormality on examination)	9; 22.5% Absent/delayed menace response (n=4) Conscious proprioceptive deficits (n=2) Reduced facial sensation (n=2) Miosis (n=2) Lateral head bobbing (n=1) Cervical ventroflexion (n=1)	9; 25.7%	0; 0%

	Ataxia (n=1) Mydriasis (n=1) Extensor spasm of limbs (n=1)		
Abdominal pain	8; 20.0%	7; 20.0%	1; 20.0%
Cardiac murmur	7; 17.5%	5; 14.3%	2; 40.0%
Collapsed	6; 15.0%	6; 17.1%	0; 0%
Bradycardia (HR<120 bpm)	4; 10%	4; 11.4%	0; 0%

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651 **Table 3.** The physical examination findings at time of referral in all cats (listed from most
652 common to least common) and then further divided into cats classified as hyponatremic
653 and/or hyperkalemic (HH) and cats classified as non-hyponatremic and non-hyperkalemic
654 (NHNH). The cat that was diagnosed in PCP did not have physical examination information
655 available; this cat was in the HH group. When this information was not available for all of the
656 remaining 40 cats, the number of cats in which the data was known is shown in the first
657 column and additionally, if this information was not available for all cats in group NHNH,
658 the number of cats in that sub-group that did have this information available is stated. Data
659 are presented as number and frequency. Significant differences ($p < 0.05$) between the HH
660 and NHNH groups are shown as *.
661 Abbreviations: HR, heart rate; RR, respiratory rate

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Clinicopathological abnormality	**All cats (n, %)**	**HH cats (n, %)**	**NHNH cats (n, %)**
Absence of a stress leukogram	25; 61.0%	23; 63.9%	2; 40.0%
Anemia	8; 19.5%	6; 16.7%	2; 40.0%
Lymphocytosis	8; 19.5%	8; 22.2%	0; 0%
Neutropenia	7; 17.1%	5; 13.9%	2; 40.0%
Eosinophilia	4; 9.8%	4; 11.1%	0; 0%
Azotemia	30; 73.2%	27; 75.0%	3; 60.0%
Increased CK (n=27; NHNH cats = 4)	18; 66.7%	17; 73.9%	1; 25.0%
Hyperkalemia	27; 65.9%	27; 75.0%	0; 0%
Hyponatremia	27; 65.9%	27; 75.0%	0; 0%
Hypochloremia (n=38)	25; 65.8%	22; 66.7%	3; 60.0%
Hyperphosphatemia (n=40)	22; 55.0%	20; 57.1%	2; 40.0%
Increased AST (n=27; NHNH cats = 2)	11; 40.7%	10; 40.0%	1; 50.0%
Increased ALT	15; 36.6%	13; 36.1%	2; 40.0%
Hyperglycemia (n=37; NHNH cats = 3)	13; 35.1%	12; 35.3%	1; 33.3%
Hypercalcemia (total and/or ionised) (n=40)	13; 32.5%	13; 37.1%	0; 0%

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Hypercalcemia based on assessment of total calcium alone (n=40)	10; 25%	10; 28.6%	0; 0%
Hypercalcemia based on assessment of ionised calcium alone (n=14; NHNH cats = 0)	8; 57.1%	8; 57.1%	n/a
Hypoalbuminemia (n=40)	12; 30%	9; 25.7%	3; 60.0%
Hypoglycemia (n=39; NHNH cats = 4)	10; 25.6%	9; 25.7%	1; 25.0%
Hypoglobulinemia (n=30)	6; 20.0%	5; 20.0%	1; 20.0%
Hyperbilirubinemia (n=37)	7; 18.9%	6; 18.8%	1; 20.0%
Increased ALKP (n=39)	7; 17.9%	6; 17.6%	1; 20.0%
Hypocholesterolemia (n=35; NHNH cats = 4)	6; 17.1%	6; 19.4%	0; 0%

Table 4. Abnormalities documented on routine hematological and biochemical testing during investigations at the PCP and RCs in all cats (listed from most common to least common for hematological alterations first and then biochemical alterations) and then further divided into cats classified as hyponatremic and/or hyperkalemic (HH) and cats classified as non-hyponatremic and non-hyperkalemic (NHNH). When the information was not available for all cats, the number of cats for which this information was available is documented in the first column and additionally, if this information was not available for all cats in group NHNH, the number of cats in that sub-group that did have this information available is stated. Cats

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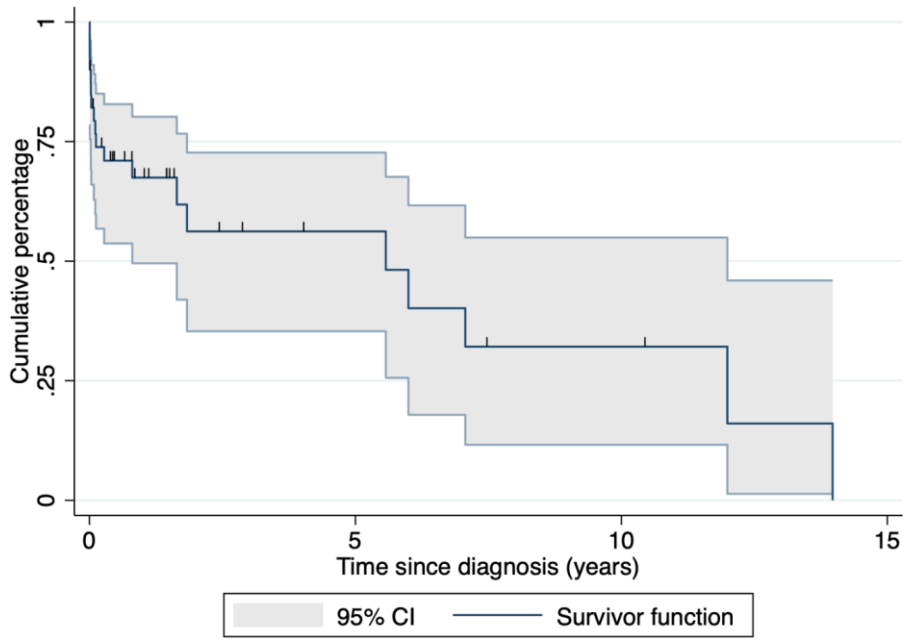
were excluded from assessment of hyperglycemia if they were known to have received glucose.

Abbreviations: AST, aspartate transaminase; ALT, alanine aminotransferase; ALKP, alkaline phosphatase; CK, creatine kinase



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689 **Figure 1.** Kaplan-Meier survival curve of all-cause mortality in cats diagnosed with
690 hypoadrenocorticism. Survival time represents the time from diagnosis in years until the time
691 of death/euthanasia due to all-cause mortality.

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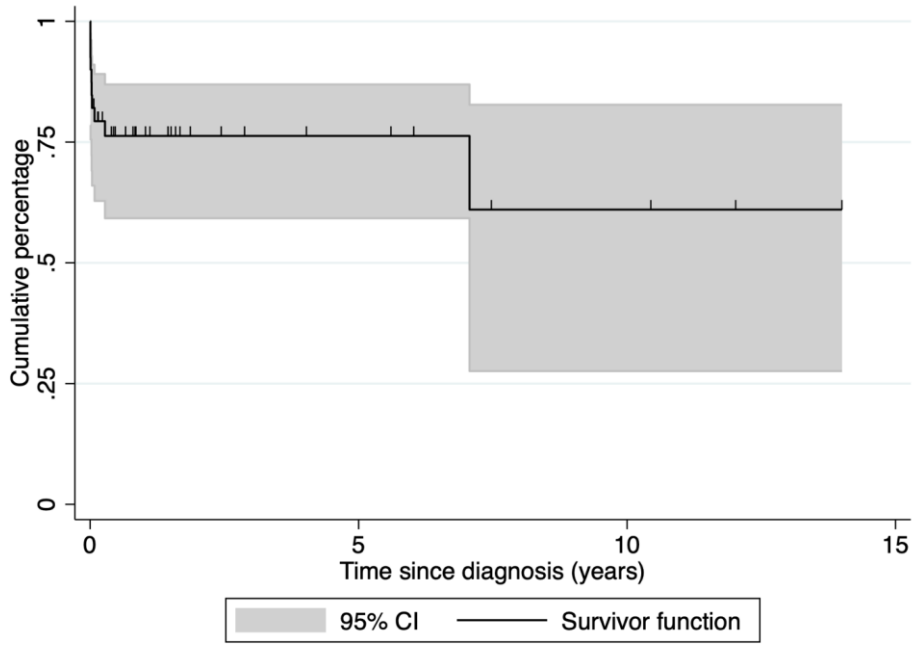

Figure 2. Kaplan-Meier survival curve of disease-specific mortality in cats diagnosed with hypoadrenocorticism. Survival time represents the time from diagnosis in years until the time of death/euthanasia due to disease-specific mortality.

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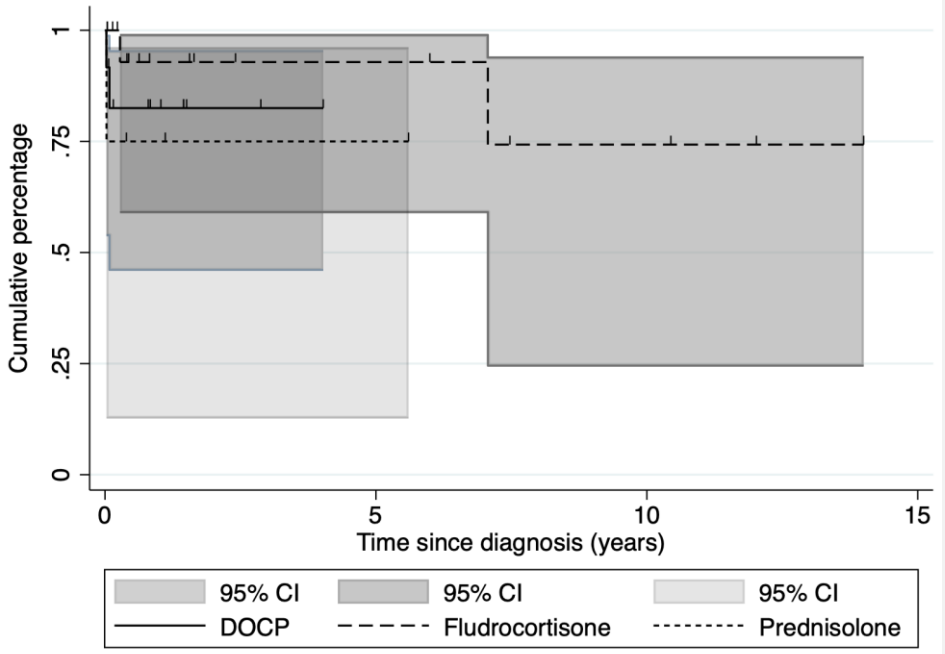

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705 **Figure 3.** Kaplan-Meier survival curve of disease-specific mortality in cats diagnosed with
706 hypoadrenocorticism, split by treatment (DOCP, FC or sole prednisolone). Survival time
707 represents the time from diagnosis in years until the time of death/euthanasia due to disease-
708 specific mortality.

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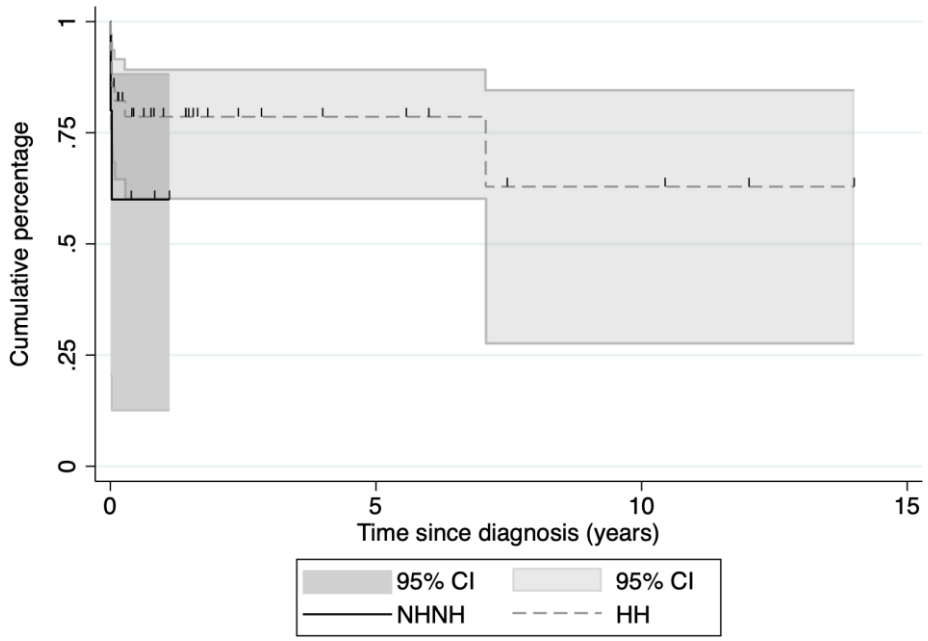

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712 **Figure 4.** Kaplan-Meier survival curve of disease-specific mortality in cats diagnosed with
713 hypoadrenocorticism, split by disease sub-type (hyponatremic and/or hyperkalemic (HH) and
714 non-hyponatremic and non-hyperkalemic (NHNH)). Survival time represents the time from
715 diagnosis in years until the time of death/euthanasia due to disease-specific mortality.

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