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

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Abstract

Background: Hypoadrenocorticism in cats is uncommonly reported. Most reports consist of cats with hyponatremia, hyperkalemia, or both.

Hypothesis/Objectives: To describe clinical findings, treatment response, and outcome in cats diagnosed with hypoadrenocorticism, including cats with abnormal and normal serum sodium and potassium concentrations.

Animals: Forty-one cats with hypoadrenocorticism; 36 with and 5 without abnormal serum sodium and potassium concentrations.

Methods: Multicenter retrospective observational study. Data for the entire cohort were assessed using descriptive statistics and differences between cats with and without abnormal serum sodium and potassium concentrations were evaluated.

Results: Median age was 5.7 years (range, 0.2-13.8). Twenty-three (56%) cats were male and 18 (44%) were female. Cats with hyponatremia, hyperkalemia, or both were less likely to have a history of vomiting ($P = .01$) but more likely to be hypothermic ($P = .03$), dehydrated ($P = .04$) or weak ($P = .04$) on examination, compared with nonhyponatremic and nonhyperkalemic cats. Frequency of hypercalcemia was 31.7%. Exocrine pancreatic insufficiency (EPI) was diagnosed in 4/7 cats tested; all 4 had concurrent cobalamin deficiency. Thirty-five (85.4%) cats survived to discharge. In 2 cats, hypoadrenocorticism occurred secondary to lymphoma. Median survival

Abbreviations: ACTHST, ACTH stimulation test; BP, blood pressure; CI, confidence interval; DOCP, desoxycorticosterone pivalate; EPI, exocrine pancreatic insufficiency; eACTH, endogenous ACTH; FC, fludrocortisone acetate; fTLI, feline trypsin-like immunoreactivity; HH, hyponatremic or hyperkalemic or both; HR, heart rate; NHNH, nonhyponatremic and nonhyperkalemic; PCP, primary care practice; RC, referral center; RR, respiratory rate; T, temperature; USG, urine specific gravity.

For affiliations refer to page 10

time (MST) for all-cause mortality was 2035 days (95% confidence interval [CI], 294-4380 days); MST for disease-specific mortality was not reached.

Conclusions and Clinical Importance: Approximately one-third of cats with hypoadrenocorticism had hypercalcemia. In some cases, hyponatremia and hyperkalemia were not observed. Cats with nonneoplastic associated hypoadrenocorticism that survive initial hospitalization can have a favorable long-term prognosis. Testing for EPI may be warranted in cats with hypoadrenocorticism.

KEYWORDS

Addison's disease, cobalamin deficiency, exocrine pancreatic insufficiency, hyperkalemia, hyponatremia, survival

1 | INTRODUCTION

Hypoadrenocorticism in cats is uncommonly reported in the veterinary literature, with most reports limited to 1 to 2 cases.[1-7] The 2 largest studies included small case numbers (10 and 11 cats), all of which had electrolyte abnormalities (hyponatremia or hyperkalemia or both).[4,5] To date, only 3 cases of cats with nonhyponatremic and nonhyperkalemic (NHNH) hypoadrenocorticism have been reported.[8-10]

Even when all reported cases were assessed together, follow-up information was limited, particularly survival times. Cats with hypoadrenocorticism have variable response to treatment but long survival times have been reported.[4,5]

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

Our primary aim was to describe the clinical findings in a large 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.

2 | MATERIALS AND METHODS

2.1 | Case selection

In this multicenter, retrospective, observational cohort study, cases of hypoadrenocorticism in cats diagnosed between January 2000 and December 2021 were evaluated. 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 had been diagnosed in primary care practice (PCP) or at a referral center (RC).

Cases were included if they had a post-ACTH serum cortisol concentration <3 μg/dL (<83 nmol/L; Supplementary Information 1).[11,12] Cats that had received PO, topical (cutaneous or inhalational) or parenterally administered short or intermediate acting corticosteroids, azole antifungal agents or progesterone hormones within 4 weeks before the ACTH stimulation test (ACTHST) were excluded, as were cats that had received long-acting corticosteroids (eg, methylprednisolone depot) in the previous 3 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 had been published previously as solitary case reports or small case series.

2.2 | Data collection

Hospital computerized databases were searched by participating centers to identify cases. Data for each case were entered into an online data-capture platform (CASTOR EDC) and, for cases that were referred, both data from the PCP and RC were included. Because of the study design on CASTOR EDC and advertised study requirements, only cases that could be included were entered into the platform. Data collected from cases included signalment, body weight at diagnosis, country and year of diagnosis, duration of clinical signs (in days) before diagnosis, clinical signs reported, clinical findings on examination, clinicopathologic findings (including ACTHST protocols used and results, plasma or serum aldosterone, and plasma eACTH measurements), systolic blood pressure results, and results of diagnostic imaging including adrenal gland size and appearance. For cats that had >1 cortisol assessment post-ACTH stimulation, the highest cortisol concentration obtained was recorded as the poststimulation result. Cases were categorized as hyponatremic and hyperkalemic (HH) if hyponatremia, or hyperkalemia or both were documented during investigations (either at the PCP or RC or both) or NHNH if hyponatremia and hyperkalemia were not documented. For all cases, treatment protocols for hypoadrenocorticism were recorded, including in-hospital and posthospitalization regimens. To assess survival times, cases were followed up until December 2022 by contact with the case veterinarian to ascertain whether for each case, the cat had died, been euthanized (and the reason for death or euthanasia if known), was still alive, or had been lost to follow-up. The last recorded treatment regimen for hypoadrenocorticism also was documented. Clinical control was documented for each case, and defined as resolution of clinical signs, electrolyte disturbances, and hypoglycemia, if present at diagnosis.

Additionally, it was recorded if any affected cat developed additional endocrine diseases after diagnosis of hypoadrenocorticism and when this diagnosis occurred. If any cats had undergone cytological or histopathological ante- or postmortem assessment of their adrenal glands or pituitary gland, this information was recorded.

2.3 | Statistical analysis

Statistical analysis was performed using commercial software (Stata). Descriptive statistics were calculated for data from the entire cohort and presented as mean (SD) for parametric continuous data and median and range for nonparametric continuous data; categorical data were presented as count and corresponding percentage. Because of multiple different laboratories and analyzers being used for blood testing, results were classified as being above, within, or below the laboratory reference range. Additionally, results of investigations by the PCP and RCs were combined (eg, if hypoglycemia was documented at either the PCP or RC or both the PCP and RC, the cat was classified as having hypoglycemia). For data comparison between cats in groups HH and NHNH, categorical variables were compared using Fisher's exact test and continuous variables with *t* tests for parametric data and Wilcoxon rank sum test for nonparametric data. Matched pairs of observations were compared using the Wilcoxon matched-pairs signed-rank test. The significance level was set at $P < .05$. For the assessment of survival, Kaplan-Meier plots were used to describe all-cause mortality and disease-specific mortality for the cohort.

3 | RESULTS

3.1 | 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 and 2010, and the remainder were diagnosed between 2011 and 2021. Forty cats were diagnosed at a RC and 1 cat was diagnosed in PCP and then referred. On evaluation of sodium and potassium results, 36 (87.8%) cats were classified as HH and 5 (12.2%) as NHNH. Four cases had been published previously in the veterinary literature.[10,14,15]

Median age at diagnosis was 5.7 years (range, 0.2-13.8). Median body weight was 3.8 kg (range, 0.88-8.2) in the 40 cats for which this information was available, and median body condition score was 4 out of 9 (range, 1-9). Twenty-three (56%) cats were male, with 1 being intact and 18 (44%) were female, with 2 being intact. No significant differences in these variables were found 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).

3.2 | Clinical signs and physical examination findings

Median duration of clinical signs before diagnosis for the entire cohort was 23 days (range, 0-365). For group HH it was 21 days (range, 0-365) and 50 days (range, 4-180) for group NHNH; this difference was not significant. Clinical signs reported are summarized in Table 2 but the most common signs, occurring in >50% of the cohort, included lethargy (87.8%), anorexia or hyporexia (78%), and weakness (61%). Only the frequency of vomiting was significantly different between groups and was higher in group NHNH ($P = .01$). Median number of clinical signs reported per cat was 5 (range, 2-8).

At the time of referral, median heart rate (HR) was 160 beats/minute (range, 60-220; n = 40), respiratory rate (RR) was 28 breaths/minute (range, 16-44; n = 34) and rectal temperature (T) was 37.1°C

TABLE 1 Descriptive statistics of the signalment of all included cases (all cats), and then further divided into cats classified as hyponatremic and hyperkalemic (HH) and cats classified as nonhyponatremic and nonhyperkalemic (NHNH).

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

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

TABLE 2 The clinical signs reported in all included cases (all cats), based on the 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 hyperkalemic (HH) and cats classified as nonhyponatremic and nonhyperkalemic (NHNH).

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%* ($P = .01$)
Diarrhea	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%
Hematochezia	1; 2.4%	0; 0%	1; 20.0%
Other	Smaller than littermate (1; 2.4%), aggression (1; 2.4%), sneezing whilst eating (1; 2.4%)	Aggression (1; 2.8%), sneezing whilst eating (1; 2.8%)	Smaller than littermate (1; 20.0%)

Note: Data are presented as number and frequency. Significant differences ($P < .05$) between the HH and NHNH groups are shown as *.

(range, 34.2-40°C; n = 36). Bradycardia (HR <120 beats/minute), tachypnea (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 most common abnormalities on examination, occurring in >50% of cases, included weakness, dehydration, and hypothermia; all 3 findings were significantly more common in cats in group HH than group NHNH (Table 3). Other examination findings are presented in Table 3.

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

3.3 | Routine laboratory findings

Findings on CBC and serum biochemistry are summarized in Table 4. The most common reported abnormalities, occurring in >50% of the cohort (when assessed), included azotemia, hyponatremia, hyperkalemia, hypochloremia, increased creatine kinase activity, and hyperphosphatemia. In the HH group, 17 (47.2%) cats were documented to have hyponatremia and hyperkalemia concurrently. The frequency of hypercalcemia (total or ionized) was 31.7%. Ionized calcium was only assessed in cats from group HH and was increased in 8/14 cases (range, 5.3-8.3 mg/dL [1.33-2.07 mmol/L]) in which it was evaluated. No significant differences were identified in the frequencies of clinicopathological abnormalities between the HH and NHNH groups, except for hyponatremia and hyperkalemia (as expected from their definition).

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 USG <1.035. For nonazotemic cats, USG ranged from 1.005 to 1.038.

Notable additional abnormalities were cobalamin and feline trypsin-like immunoreactivity (fTLI) results. Serum cobalamin concentration 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 (3 cats in group HH and 2 cats in group NHNH) and exocrine pancreatic insufficiency (EPI) in 4/7 (57.1%); all cases had weight loss or gastrointestinal tract signs reported.[10] All cats with cobalamin deficiency had undergone fTLI assessment and 4 were diagnosed with concurrent EPI; 3 of these cats also were suspected to have a chronic enteropathy based on ultrasonographic findings (diffuse thickening of the muscularis propria with or without thickening of the submucosa). The remaining cat with cobalamin deficiency also was diagnosed with a suspected chronic enteropathy. None of the 5 cats had gastrointestinal tract biopsies performed at the time of hypoadrenocorticism diagnosis.

TABLE 3 Physical examination findings at the time of referral in all cats (listed from most common to least common) and further divided into cats classified as hyponatremic and hyperkalemic (HH) and cats classified as nonhyponatremic and nonhyperkalemic (NHNH).

Clinical examination finding	All cats (n, %)	HH cats (n, %)	NHNH cats (n, %)
Hypothermia (<37.8°C) (n = 36)	24; 66.7%	23; 74.2%*	1; 20.0%* (*P* = .03)
Dehydrated	26; 65.0%	25; 71.4%*	1; 20.0%* (*P* = .04)
Weakness	26; 65.0%	25; 71.4%*	1; 20.0%* (*P* = .04)
Tachypnea (RR >30 bpm) (n = 34; NHNH cats = 4)	10; 29.4%	9; 30.0%	1; 25.0%
Neurological abnormalities (4 cats had more than 1 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) Ataxia (n = 1) Mydriasis (n = 1) Extensor spasm of limbs (n = 1)	9; 25.7%	0; 0%
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%

Note: The cat that was diagnosed in PCP did not have physical examination information available; this cat was in the HH group. When this information was not available for all of the remaining 40 cats, the number of cats in which the data was known is shown in the first column and additionally, if this information was not available for all cats in group NHNH, the number of cats in that subgroup that did have this information available is stated. Data are presented as number and frequency. Significant differences ($P < .05$) between the HH and NHNH groups are shown as *.
Abbreviations: HR, heart rate; RR, respiratory rate.

3.4 | Testing for hypoadrenocorticism

Testing occurred a median of 2 days after referral (range, 0-30). Basal cortisol concentration was utilized as an initial screening test in 12 cats and was undetectably low in 7. Timings of cortisol testing post-ACTH stimulation are shown in Supplementary Information 2. Post-ACTH-stimulation cortisol concentrations were undetectably low in 22 cats. In the remaining 19 cats, the median concentration was 0.9 µg/dL (24.8 nmol/L; range, 0.1-1.8 µg/dL). Aldosterone concentrations were assessed in 11 cats (including 2 cats from group NHNH), 5 of which had aldosterone assessed both pre- and post-ACTH stimulation. All 11 cats had aldosterone concentrations below laboratory reference ranges or concentrations that were undetectably low. Plasma eACTH concentrations were assessed in 13 cats including 1 in group NHNH. For 9 cases, the eACTH concentration was recorded as being above the upper limit of detection for the utilized assay (≥600 pg/mL [n = 1] and ≥1250 pg/mL [n = 8]) and for the other 4 cats it ranged from 1218 to 1494 pg/mL. Aldosterone and eACTH concentrations, where assessed, were suggestive of those cases being caused by primary hypoadrenocorticism.

Two cats received glucocorticoid treatment before diagnosis (0.1 mg/kg dexamethasone 28 days before the ACTHST and an unknown dose of dexamethasone 21 days before the ACTHST) and for 3 cats, information on previous corticosteroid treatment was unknown. In all 5 cats, plasma eACTH concentrations were ≥1218 pg/mL.

3.5 | Imaging

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

3.6 | Thoracic imaging

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

3.7 | Adrenal gland imaging

Abdominal imaging was performed in 37 cats; 33 had ultrasonography, 3 had ultrasonography and radiography, and 1 had ultrasonography and computed tomography. Adrenal gland size, 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 2 cats, lymphoma affecting the adrenal glands was documented at necropsy. For these cats, 1 had adrenal widths of 8 mm bilaterally and, in the other, the adrenal glands were replaced by a mass measuring 8 × 5 cm. For the remaining cats, the median width of the right adrenal

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 hyperkalemic (HH) and cats classified as nonhyponatremic and nonhyperkalemic (NHNH).

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 or ionized, or both) (n = 40)	13; 32.5%	13; 37.1%	0; 0%
Hypercalcemia based on assessment of total calcium alone (n = 40)	10; 25%	10; 28.6%	0; 0%
Hypercalcemia based on assessment of ionized 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%

Note: 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 subgroup that did have this information available is stated. Cats were excluded from the assessment of hyperglycemia if they were known to have received glucose.
Abbreviations: ALKP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; CK, creatine kinase.

gland was 2.8 mm (range, 1.5-6) and in 4 cats the adrenal gland could not be seen. The median width of the left adrenal gland was 3 mm (range, 1.7-5.4) but it could not be seen in 3 cats. Adrenal gland echogenicity was reported as normal in most cases but there were 2 cases each in which a hyper- and hypoechoic appearance was reported and 2 separate cats had evidence of adrenal gland mineralization.

3.8 | Treatment of hypoadrenocorticism

In-hospital glucocorticoid and 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 fludrocortisone acetate (FC; n = 19); most cats received a combination of treatments.

Intravenous fluid therapy was administered to 90.2% (n = 37) of cats at the RCs. One cat required 2 packed red blood cell transfusions because of the development of marked anemia during hospitalization.

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 6 cats (14.6%), 1 died from cardiopulmonary arrest, and 5 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 duration postdiagnosis was 4 days (range, 0-10). For cats that did not survive to discharge, hospitalization duration before death or euthanasia ranged from 2 to 13 days postdiagnosis.

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 4 cats in group NHNH were started on prednisolone (n = 3) or prednisolone and DOCP (n = 1); the latter cat had documented hypoaldosteronism. Median starting dosage of FC was 0.02 mg/kg/day (range, 0.01-0.14) and in 8 cats treatment was divided twice daily. Starting dosage 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 cats diagnosed before 2016 were started on DOCP compared to 71.4% of cats diagnosed from 2016 until 2021.

One HH cat initially started on FC was changed to DOCP 10 months postdiagnosis because of inability to control serum electrolyte concentrations. Another HH cat initially started on prednisolone alone had DOCP treatment added 1 month postdiagnosis because of recurrence of hyperkalemia.

Clinical control for cats surviving hospitalization was achieved a median of 5 days postdiagnosis (range, 1-247); 2 cats were not stabilized before euthanasia at 10 and 40 days postdiagnosis.

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 dosages 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 dosage for DOCP was 2.2 mg/kg (range, 1.3-3), with 4 cats requiring dose escalation, 3 cats a dose decrease, and 3 cats remaining at the starting dose; 4 cats required administration more frequently than every 28 to 30 days (at 21-25 day intervals). There was only a significant difference between the starting and final dose for prednisolone ($P = .01$).

3.9 | Follow-up

Median follow-up period of the entire cohort was 287 days (range, 0-5103). At the end of follow-up for all cats, 12 (29.3%) were still alive, 6 (14.6%) had died, 14 (34.1%) had been euthanized and 9 (22%) were lost to follow-up. Of the 4 NHNH cats that survived hospitalization, 2 were euthanized at 10 and 298 days postdiagnosis, 1 was lost to follow-up 133 days postdiagnosis and 1 cat was still alive 395 days postdiagnosis. No NHNH cats treated with prednisolone alone were documented to develop hyponatremia or hyperkalemia or both during follow-up (median, 133 days; range, 10-395). Of the 31 HH cats that survived hospitalization, 7 were euthanized at a median of 670 days postdiagnosis (range, 30-5103), 5 cats died at a median of 600 days postdiagnosis (range, 9-4380), 8 cats had been lost to follow-up at a median of 110 days postdiagnosis (range, 4-1460), and 11 cats were still alive at a median of 539 days postdiagnosis (range, 280-3803).

Of the cats that died or were euthanized during posthospitalization follow-up, 5 deaths were attributed to hypoadrenocorticism: aspiration pneumonia suspected secondary to vomiting or neurological deterioration (weakness) or both (n = 2), relapse of clinical signs (n = 1), cardiac arrest associated with the owner not administering medication (n = 1), and lymphoid neoplasia as the cause of hypoadrenocorticism (n = 1). For the other 9 cats, causes were not directly attributed to hypoadrenocorticism and included gastrointestinal tract neoplasia (n = 2), unknown (n = 2) and 1 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% confidence interval [CI], 294-4380 days; Figure 1) but MST for disease-specific mortality was not 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 were not significantly different between cats treated with DOCP (did not 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 3 treatment groups reached MST preventing statistical comparisons (Figure 3). The difference in median all-cause mortality between cats in group HH and cats in group NHNH was not significant and for disease-specific mortality, MST was not reached (Figure 4).

3.10 | Development of endocrine disease on follow-up

One cat developed hyperthyroidism 2373 days postdiagnosis, and 1 cat developed diabetes mellitus 135 days postdiagnosis.[10]

3.11 | Adrenal or pituitary gland cytology and histopathology

Necropsy histopathology of the adrenal glands was performed in 7 cats; adrenal gland cytology or assessment of the pituitary gland

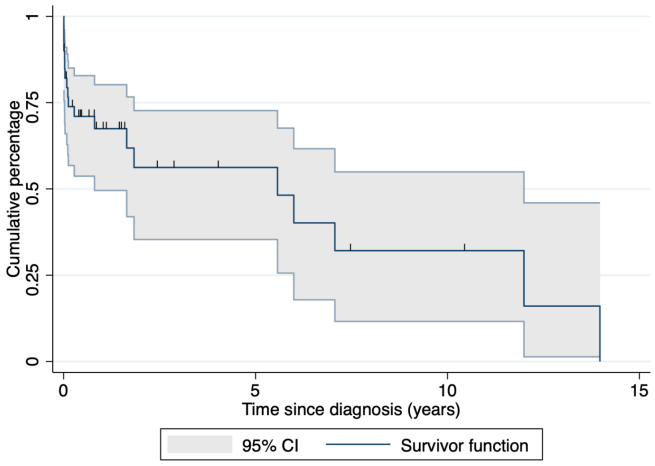

FIGURE 1 Kaplan-Meier survival curve of all-cause mortality in cats diagnosed with hypoadrenocorticism. Survival time represents the time from diagnosis in years until the time of death or euthanasia because of all-cause mortality.

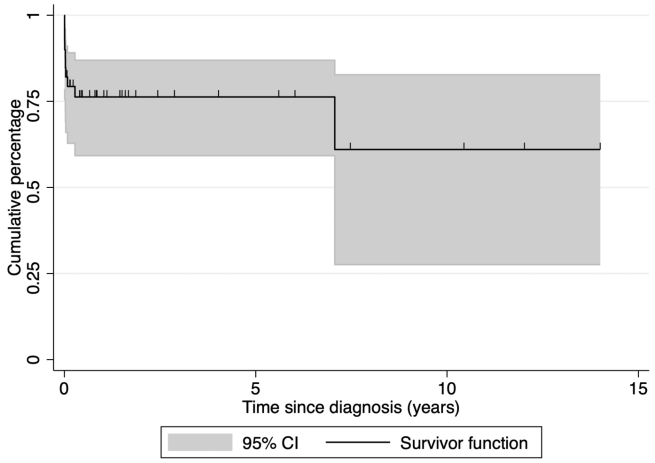

FIGURE 2 Kaplan-Meier survival curve of disease-specific mortality in cats diagnosed with hypoadrenocorticism. Survival time represents the time from diagnosis in years until the time of death or euthanasia because of disease-specific mortality.

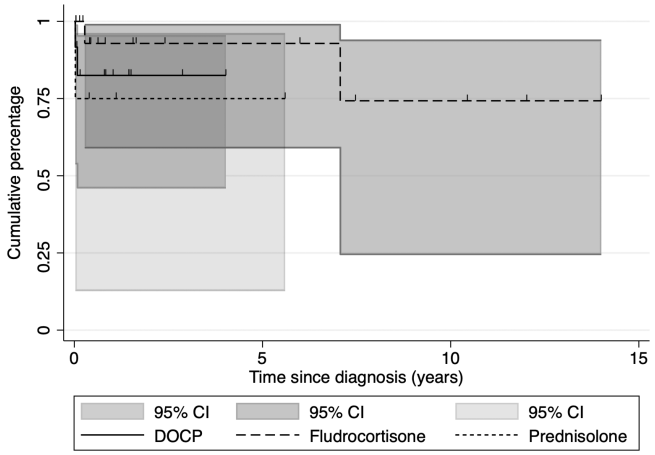

FIGURE 3 Kaplan-Meier survival curve of disease-specific mortality in cats diagnosed with hypoadrenocorticism, split by treatment (DOCP, FC, or sole prednisolone). Survival time represents the time from diagnosis in years until the time of death or euthanasia because of disease-specific mortality.

was not performed in any cat. In 2 cats, euthanized at 2 and 30 days postdiagnosis, large cell lymphoma was documented as the cause of hypoadrenocorticism. In the other 5 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]

4 | DISCUSSION

Our study provides comprehensive documentation of the clinical presentation, diagnostic test results, treatment, and outcome of cats diagnosed with hypoadrenocorticism. Our results support previous findings, including the possibility of a breed predisposition for British

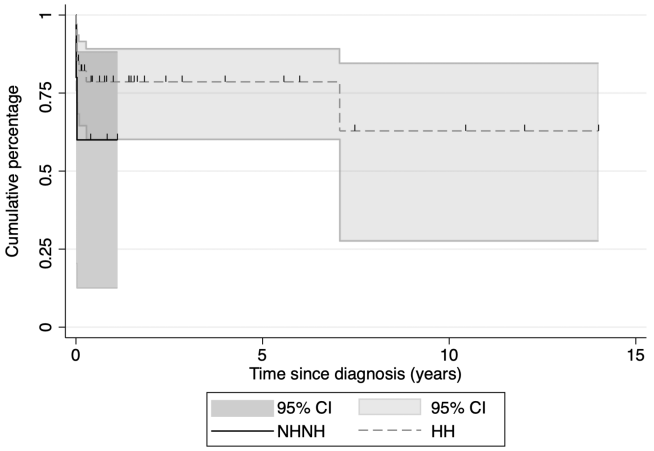

FIGURE 4 Kaplan-Meier survival curve of disease-specific mortality in cats diagnosed with hypoadrenocorticism, split by disease subtype (hyponatremic and hyperkalemic (HH) and nonhyponatremic and nonhyperkalemic (NHNH)). Survival time represents the time from diagnosis in years until the time of death or euthanasia because of disease-specific mortality.

shorthaired cats and a higher required starting dose of DOCP compared with dogs. Our study also demonstrated a higher than previously reported prevalence of hypercalcemia, and concurrent presence of EPI and cobalamin deficiency in several cases of hypoadrenocorticism.

In dogs, certain breeds are at an increased risk of developing hypoadrenocorticism, but in cats risk has been harder to discern because of the limited number of cases published in the literature.[16-18] An increased prevalence in British shorthairs has been proposed in a recent study, because 54.5% of the study population (11 cats) were of this breed.[4] Additionally, 3 further case reports of British shorthair cats with hypoadrenocorticism have been published.[1,19,20] In our study population, the percentage of British shorthairs (approximately 10%) was not 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 2 studies could be the different population sizes and degree of interbreeding of British shorthairs among countries, because our study included cats from around the world, rather than just a single country. However, given this growing database, breed could help increase the index of suspicion for hypoadrenocorticism.[21]

Our study provided findings for 5 cats without hyponatremia and hyperkalemia. Two cats underwent aldosterone testing, with 1 additionally having eACTH assessment. In both cases, results were supportive of primary hypoadrenocorticism. Only 3 previous NHNH cases have been reported in cats; 1 had secondary hypoadrenocorticism, 1 had corticosteroids administered before diagnosis and an eACTH was not performed to exclude pituitary suppression secondary to corticosteroid administration and the third case was included in our study population.[8-10] However, our documentation of 4 additional NHNH cases provides further evidence that hypoadrenocorticism in cats should be considered as a differential diagnosis in relevant cases, regardless of typical expected electrolyte changes, as

has been shown in dogs.[22-24] In contrast to what has been documented in dogs, none of the NHNH cats treated with prednisolone alone developed hyponatremia or hyperkalemia on follow-up, but 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 postdiagnosis.[25,26] Based on the number of NHNH cats included and the relatively short median follow-up time, there are insufficient data to determine if ongoing electrolyte monitoring is necessary in cats started only on glucocorticoid supplementation and for how long postdiagnosis monitoring should be carried out.

Few studies have directly compared HH dogs to NHNH dogs 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 were not seen in our study, which may have been because of the small number of NHNH cats included. However, only HH cats were documented to be hypercalcemic. The frequency of hypercalcemia noted in cats in our study (31.7%) was higher than that previously documented for cats in the veterinary literature (approximately 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 with other studies in which only serum total calcium concentrations were reported. Based on our findings, the presence of hypercalcemia could increase suspicion of hypoadrenocorticism and demonstrates that hypoadrenocorticism should be considered as a differential diagnosis in hypercalcemic cats.[28]

An interesting finding in our study was the documentation of cobalamin deficiency with or without concurrent EPI in 5 cases, including 1 previously published case.[10] In dogs, cobalamin deficiency occurs in up to 18.2% of NHNH cases, and proposed causes have included a concurrent enteropathy or a direct link to hypoadrenocorticism.[23] In our study, cobalamin deficiency was documented in both groups. Causes were attributed to concurrent presence of EPI or chronic enteropathy, but a direct consequence of hypoadrenocorticism could not be definitively excluded. In humans, a link exists between hypoadrenocorticism and the autoimmune condition pernicious anemia, with the latter occurring secondary to a deficiency or 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] Exocrine pancreatic insufficiency in cats is attributed typically to pancreatitis, which in most cases is presumed to be idiopathic, although autoimmune causes cannot be excluded. Therefore, it is possible that similar to humans, concurrent autoimmune disease may be present, resulting in a lack of intrinsic factor and subsequent cobalamin deficiency in some cats with hypoadrenocorticism.[10,31-33] Because cobalamin status was only assessed in 26.8% of the population and fTLI in 17.1%, the prevalence of cobalamin deficiency and 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 hypoadrenocorticism. Ultrasonography in both cases showed a mass replacing the adrenal glands or adrenomegaly. These findings emphasize the importance of performing abdominal imaging as part of the diagnostic evaluation in cats with hypoadrenocorticism to screen for lymphoma as a possible cause.

Similar to dogs, historically cats with HH hypoadrenocorticism were more commonly treated with FC with or without prednisolone compared with DOCP and prednisolone.[5,19,34-37] However, because DOCP has been documented to be more effective in suppressing plasma renin activity than FC, combined with the availability of a formulation of DOCP licensed for dogs in Europe, most dogs diagnosed recently are treated with DOCP and prednisolone, and the same trend has been seen in cats.[4,38-40] This trend was found in our study with 11.8% of cats diagnosed before 2016 being started on DOCP for mineralocorticoid replacement compared with 71.4% of cats diagnosed from 2016 to 2021. Despite this trend, no significant difference in MST was found between cats treated with FC vs DOCP in our study when assessing all-cause mortality. However, this finding may have been biased by cats treated with DOCP having shorter follow-up times because of when they were diagnosed. Further assessment would require analysis of disease-specific mortality, which was not possible in our study because of MSTs not being reached by the end of the study period, and utilization of a randomized controlled trial.

Studies in dogs have documented that starting dosages of DOCP (1.1 and 1.5 mg/kg) lower than recommended by the manufacturer (2.2 mg/kg) appear to be more appropriate in most cases.[39,41,42] However, in contrast, a starting dosage of 2.2 mg/kg has been advised in cats because 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 recommendation because our median final dosage was similar at 2.2 mg/kg and all 3 cats started on doses <2.2 mg/kg required dose escalation.

Our study documented the long-term prognosis of cats with hypoadrenocorticism to be favorable, 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 documented in dogs, suggesting that cats either may be diagnosed at a later stage of the disease or be more difficult to stabilize.[43-45] This difficulty in stabilization could be a consequence of their higher requirement for mineralocorticoids and glucocorticoids or the presence of concurrent disease as was noted in several cats in our study, which may have impacted their response to treatment.[4] Increased difficulty stabilizing these patients was further evidenced by the longer hospitalization times in our cohort, which paralleled those previously reported in the veterinary literature, compared with that documented for dogs.[4,44,45] However, because in-hospital treatment was not standardized, treatment as a confounding factor could not be excluded. This potential difference between cats and dogs with hypoadrenocorticism should be considered when assessing initial clinical response to treatment after diagnosis.

Our study had some limitations. The main limitations were its retrospective and multicenter design. This feature resulted in multiple laboratories being utilized, preventing assessment and comparison between groups of specific laboratory results, a lack of standardized investigations and treatment, missing data, and the number of cases lost to follow-up. These limitations may have influenced some of our findings, especially assessment of the number of cats with EPI and cobalamin deficiency and the survival and outcome data.

For our inclusion criteria, we elected to use a higher cut-off for post-ACTH cortisol concentrations than previously utilized in studies of cats. This cut-off was used to address the possible variation in cortisol measurements among 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 clinical signs.[11,12,46] This approach could have resulted in some ambiguous cases being included. However, because all cases included had post-ACTH cortisol concentrations lower than the standard cut-off of <2 μg/dL (<55 nmol/L), this factor was not considered a concern.

Although our study was open to centers worldwide (including PCPs and RCs) and a 21-year time period was utilized to increase case numbers, the number of cats included still was relatively small and not comparable to case numbers documented in studies on hypoadrenocorticism in dogs.[27,34] This finding supports the rarity of this condition in cats and the fact that this disease is rarely tested for.

Four cats were included that had been published previously as case reports or case series. This number totalled <10% of the study population, and their inclusion strengthened our findings (ie, documentation of EPI in several new cases, along with the previously reported case that was included), and we identified the previously published cases. Thus, their inclusion should not have negatively impacted or biased our findings.

Cases were classified as NHNH based solely on serum electrolyte concentrations, because aldosterone concentrations were not assessed in all cases and thus some cats still may have been mineralocorticoid deficient; which was unavoidable because of the retrospective study design. Possible miscategorization also has been documented as a limitation in previous studies in dogs because aldosterone has not always been measured in retrospective studies as a consequence of lack of laboratory availability of this test or associated costs.[26,27] The small number of NHNH cats may have confounded our results when assessing statistical differences with the HH group. Therefore, findings relating to comparison of these 2 groups should be interpreted with caution.

In conclusion, we identified that cats with hypoadrenocorticism can present with or without hyponatremia and hyperkalemia, demonstrating that this condition should be considered in cats presenting with suggestive clinical signs and physical examination findings, regardless of serum electrolyte concentrations. A higher than previously reported frequency of hypercalcemia was identified and, as such, its presence can help increase the clinical index of suspicion for hypoadrenocorticism. Given the occurrence of cobalamin deficiency with or without EPI in several cats in our study, assessment for cobalamin deficiency and EPI may be warranted in cats diagnosed with hypoadrenocorticism. Our study suggests screening for lymphoma as a cause of hypoadrenocorticism is advisable in cats. Cats with non-neoplastic associated hypoadrenocorticism that survive initial hospitalization have a favorable long-term prognosis.

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CONFLICT OF INTEREST DECLARATION

Emma Roberts—Consultancy: Dechra. Federico Fracassi—Financial support, speaking, and consultancies: Dechra. Ian Ramsey—Speaking and consultancies: Dechra. Imogen Schofield—Consultancy: Dechra. Carolina Arenas—Consultancy: Dechra. No other authors declare a conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Approved by the Royal College of Veterinary Surgeons ethics review panel (2022-029-Roberts).

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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