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Comparison of Survival Times for Dogs with Pituitary-Dependent Hyperadrenocorticism in a Primary-Care Hospital: Treated with Trilostane versus Untreated

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Background: Although pituitary-dependent hyperadrenocorticism (PDH) is one of the most common endocrinopathies in dogs, the effects of withholding treatment on survival time in dogs with PDH remain unclear.

Hypothesis/Objectives: The purpose of this study was to clarify the effects of treatment in dogs with PDH by comparing survival times between dogs treated with trilostane and untreated dogs.

Animals: Forty-three dogs diagnosed with PDH at a primary-care hospital in Japan between June 2009 and January 2014.

Methods: Retrospective cohort study. The medical records of dogs with PDH treated with trilostane (n = 17) or left untreated (n = 26) were reviewed retrospectively. Survival analysis at 2 years after diagnosis of PDH was performed.

Results: Median survival time for the trilostane group was not reached (95% confidence interval [CI], 443 days–not applicable) and was significantly longer than the 506 days (95% CI, 292–564 days; $P = .016$) for the untreated group. Multivariate Cox proportional hazards analysis (including age at diagnosis, basal cortisol concentration at diagnosis, and treatment group) only identified assignment to the untreated group (hazard ratio, 5.01; 95% CI, 1.63–15.44) as associated with increased mortality.

Conclusions and Clinical Importance: The results of this retrospective cohort study suggest that withholding treatment for dogs with PDH might be associated with a higher risk of death. This represents the largest study to date to report survival times of untreated dogs with PDH.

Key words: Canine; Hypercortisolism; Prognosis.

Hyperadrenocorticism is one of the most common endocrinopathies in dogs, with an estimated prevalence of 0.28% in a recent UK study.[1] Among dogs with hyperadrenocorticism, pituitary-dependent hyperadrenocorticism (PDH) accounts for about 80%.[2] Excessive secretion of ACTH can cause bilateral adrenal hyperplasia and hypersecretion of glucocorticoids, leading to a number of nonspecific clinical signs.[2] Although PDH is potentially associated with life-threatening complications such as pulmonary thromboembolism,[3–5] acute pancreatitis,[6,7] hypertension,[8,9] proteinuria,[8,10–13] infectious diseases,[14] diabetes mellitus,[15–17] and gallbladder mucoceles,[18] no previous studies have investigated survival times in a large number of untreated dogs. The effect of withholding treatment on survival time in dogs with PDH has thus remained unclear. Despite the lack of information on survival benefits, this disease is usually treated because of the unfavorable clinical signs, such as polyuria and polydipsia, skin manifestations, and panting, and thus, there is a perception that withholding treatment would be unethical. In primary-care hospitals, however, our experience has shown that the owners of dogs with PDH, regardless of the clinical signs, often decline treatment because of the financial burden, deterioration of quality of life mainly related to the side effects of treatment, and a lack of information on whether survival would be prolonged.

Currently, PDH in dogs is usually treated medically to ameliorate clinical signs, despite this approach not being curative. Pituitary gland surgery has proven effective in dogs with PDH,[19] but can be performed only in specialized veterinary institutions.[2] Trilostane (4,5-epoxy-17-hydroxy-3-oxoandrostane-2-carbonitrile) has recently become one of the preferred treatment choices for dogs with PDH. This drug is a competitive inhibitor of the 3β-hydroxysteroid dehydrogenase-isomerase enzyme

Abbreviations:

ALP	alkaline phosphatase
ALT	alanine aminotransferase
CI	confidence interval
HDDST	high-dose dexamethasone suppression test
HR	hazard ratio
IQR	interquartile range
LDDST	low-dose dexamethasone suppression test
PDH	pituitary-dependent hyperadrenocorticism
post-ACTH cortisol	cortisol concentrations after ACTH stimulation
pre-ACTH cortisol	cortisol concentrations before ACTH stimulation
UCCR	urinary corticoid-to-creatinine ratio

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system and its efficacy and safety have been reviewed elsewhere.[20]

The purpose of the study reported here was to clarify the effects of treatment in dogs with PDH by comparing survival times between dogs treated with trilostane and untreated dogs. The hypothesis of this study was that a significant difference in survival time would be seen between dogs treated with trilostane and untreated dogs.

Materials and Methods

Study Design

A retrospective cohort study in dogs was performed at a primary-care hospital in Japan (Yuki Animal Hospital).

Cases

The medical records of all dogs that had been newly diagnosed with spontaneous hyperadrenocorticism between June 2009 and January 2014 were evaluated. A criterion for inclusion was diagnosis of PDH, and dogs were classified into 2 groups depending on treatment: dogs treated with trilostane (trilostane group); and dogs that remained untreated (untreated group). Dogs were excluded if a complete diagnosis was not achieved, if the dog was diagnosed with adrenal-dependent hyperadrenocorticism, if the dog underwent treatment for PDH other than trilostane, or if the dog received medications that would be expected to alter cortisol concentrations, such as ketoconazole (Fig 1). Concurrent disorders were not exclusion criteria in this study.

Suspicion of hyperadrenocorticism was based on history, clinical examination, a complete blood cell count, biochemical profile, urinalysis, radiography, and ultrasonography. Dogs were included if they had at least 1 clinical sign of hyperadrenocorticism as described in the ACVIM consensus statement.[21] ACTH stimulation tests were conducted in all dogs to determine cortisol concentrations before (pre-ACTH cortisol) and 1 or 2 hours after (post-ACTH cortisol) IM or IV administration of 0.125 or 0.25 mg of tetracosactide acetate.[a] Hyperadrenocorticism was diagnosed if the post-ACTH cortisol was ≥20 μg/dL.[21,22] Additionally, in some cases, a low-dose dexamethasone suppression test (LDDST) was performed (n = 5) or the urinary corticoid-to-creatinine ratio (UCCR) was determined (n = 3). For the LDDST, cortisol concentrations were determined before and 4 and 8 hours after IV administration of 0.01 mg/kg of dexamethasone.[b] Hyperadrenocorticism was diagnosed if the cortisol concentration was >1.4 μg/dL at 8 hours.[21,22] For UCCR, urine samples collected by owners at home in the morning were evaluated as described previously.[22] Hyperadrenocorticism was diagnosed for UCCR $>60 \times 10^{-6}$.[21,22] Serum[c] and urine[d] cortisol concentrations were measured at commercial laboratories using a chemiluminescent enzyme immunoassay[e] that has been validated for dogs.[23–25] Because the cutoff values of post-ACTH cortisol and cortisol concentrations at 8 hours for LDDST were not established by the laboratory, these were determined with reference to a past report which used the chemiluminescence system.[22] The cutoff value of UCCR was also obtained from that report.[22]

Differentiation of PDH was conducted on the basis of the shape of the adrenal glands on ultrasonography, and the results of the LDDST, high-dose dexamethasone suppression test (HDDST),

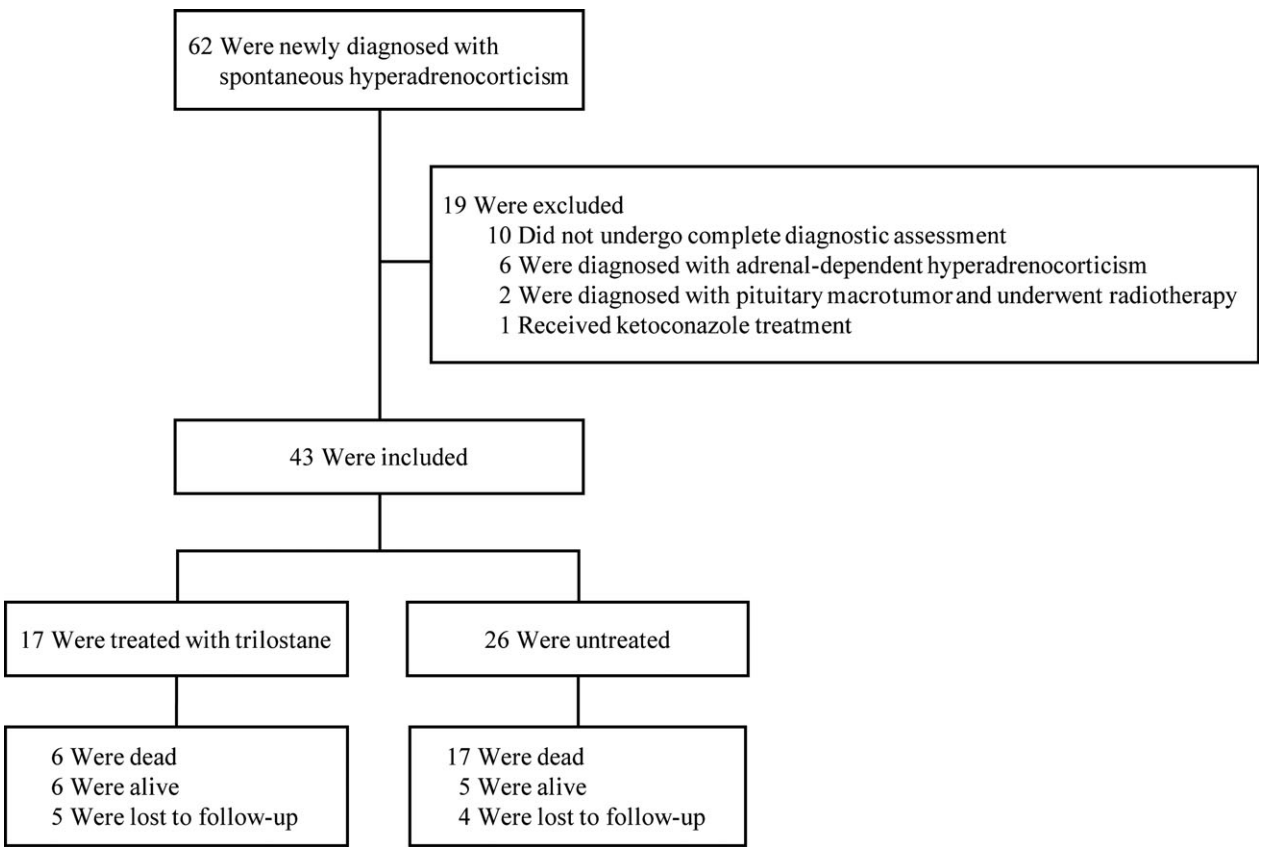

Fig 1. Flowchart of cases.

and endogenous ACTH plasma concentration assay. For the HDDST, cortisol concentrations were determined before and 4 and 8 hours after IV administration of 0.1 mg/kg of dexamethasone. Adrenal ultrasonography was conducted in all dogs and measurements were taken and recorded when performed. PDH was diagnosed if normal-sized or enlarged adrenal glands were recognized bilaterally, or enlarged adrenal glands with loss of the normal structure were not recognized on ultrasonography.[21,26,27] To help in the differentiation of PDH, particularly in dogs with equivocal adrenal asymmetry on ultrasonography, the HDDST was performed (n = 30) and/or endogenous ACTH plasma concentration was determined (n = 28). PDH was diagnosed if cortisol concentration was suppressed (<50% of basal cortisol concentration at 4 or 8 hours in LDDST or HDDST) or endogenous ACTH plasma concentration was >5 pg/mL.[21,28,29] Endogenous ACTH plasma concentrations[c] were measured at commercial laboratories by means of a chemiluminescent enzyme immunoassay[e] that has been validated for dogs.[30]

From the medical records, breed, age at diagnosis, weight at diagnosis, sex, alanine aminotransferase (ALT) activity at diagnosis, alkaline phosphatase (ALP) activity at diagnosis, results of ACTH stimulation tests (pre- and post-ACTH cortisol) at diagnosis, clinical signs, number of visits to the hospital (apart from the monitoring visits), cost of all treatments (apart from the cost of trilostane and its monitoring), date of diagnosis, and date of death were obtained. Date of diagnosis was defined as the day of the first ACTH stimulation test because this test was conducted in all dogs when hyperadrenocorticism was initially suspected. The cause of death or reason for euthanasia was also recorded.

The primary outcome was death from any cause, and survival time was defined as the time between date of diagnosis and date of death. Follow-up was up to 2 years. Dogs that remained alive as of the most recent follow-up were censored as of the last date they were reported to be alive. Dogs that remained alive at 2 years after diagnosis of PDH were also censored.

Based on clinical signs, adverse effects of treatment, and cost of treatment, whether to treat a dog that had been diagnosed with PDH was determined by the clinician and the owner. For treatment, initial doses of trilostane (Vetoryl[f] or Adrestan[g]) were given 1–3 mg/kg PO once or twice daily. In accordance with the instructions from the manufacturer, dogs treated with trilostane were principally evaluated by clinical signs and ACTH stimulation tests after treatment, and then, the dose and frequency of trilostane were adjusted. For monitoring, ACTH stimulation tests were conducted 4–6 hours after trilostane administration. The goal of treatment was to achieve a post-ACTH cortisol of 1.5–9.1 μg/dL, along with improvement of clinical signs. If post-ACTH cortisol was well controlled (1.5–5.4 μg/dL), but no improvement of clinical signs was achieved, the frequency of trilostane administration was increased. If the post-ACTH cortisol was <1.5 μg/dL or side effects were apparent, the dose of trilostane was decreased or administration was suspended.

Statistical Analysis

Differences between the trilostane and untreated groups were compared using Fisher's exact test for categorical variables and the Mann–Whitney *U*-test for continuous variables. Survival curves were generated using the Kaplan–Meier product-limit method with comparisons between curves on the log-rank test. In a multivariate analysis, Cox proportional hazards modeling was used with time to death as the objective variable and treatment group as the explanatory variable. In addition to treatment group, variables such as age and pre-ACTH cortisol were included as continuous variables. For each variable, the assumption of constant proportional hazards was tested by the evaluation of Schoenfeld residuals. Because not all dogs in the trilostane group continued treatment until the final follow-up, survival analysis was conducted using 2 methods. In a primary analysis, outcomes were compared between all dogs initially treated with trilostane and all dogs left untreated. In a secondary analysis, dogs that stopped trilostane treatment were censored from survival analysis on suspension of treatment; then, outcomes were compared. As we supposed that dogs in the untreated group might have been treated less often for other concurrent illnesses due to the unwillingness of the owners to have them treated for other conditions and therefore more likely to die sooner, the number of visits to the hospital (apart from monitoring visits) and the cost of all treatments (apart from the cost of trilostane and its monitoring) between the groups were compared. In addition, because the untreated group might have shown fewer or less severe clinical signs to warrant treatment, rates of clinical signs were also compared.

All statistical analyses were performed using EZR software, which is a graphical user interface for R.[31] This modified version of R Commander includes functions frequently used in biostatistics. Values of $P < .05$ were considered statistically significant.

Results

Of the 62 dogs newly diagnosed with spontaneous hyperadrenocorticism, 43 with PDH were included in the study. Ten dogs were excluded because the complete diagnostic assessment was not achieved, 6 were excluded because of the diagnosis of adrenal-dependent hyperadrenocorticism, 2 were excluded because they were diagnosed with pituitary macrotumor and underwent radiotherapy before initiating trilostane treatment, and 1 dog was excluded because the dog received ketoconazole treatment (Fig 1).

There were 17 dogs in the trilostane group. At the date of censoring, 6 dogs (35%) were dead, 6 (35%) were alive, and 5 (29%) had been lost to follow-up. During the study period, 4 dogs discontinued treatment after 110, 223, 225 and 563 days. The reasons for discontinuation were cost for 2 dogs, side effects for 1 dog, and concurrent disease (gastrointestinal stromal tumor) for 1 dog. The untreated group comprised 26 dogs. As of the date of censoring, 17 dogs (65%) were dead, of which 1 dog had been euthanized, 5 (19%) were alive, and 4 (15%) had been lost to follow-up (Fig 1).

Baseline characteristics according to treatment are summarized in Table 1. No significant differences were seen between groups except for pre-ACTH cortisol. Median pre-ACTH cortisol was significantly higher in the trilostane group than in the untreated group (11.2 μg/dL versus 4.7 μg/dL; $P = .006$). There was no significant difference in the number of visits to the hospital, cost of all treatments, and rate of clinical signs between the 2 groups. The trilostane group included 10 spayed females, 5 intact males, and 2 neutered males. The untreated group included 7 intact females, 11 spayed females, 4 intact males, and 4 neutered males. The common clinical signs reported at diagnosis were hepatomegaly (58%), polyuria and polydipsia (42%), abdominal distension (33%), alopecia (28%), and panting (14%).

Twelve breeds were represented. Breeds in the trilostane group included Mongrel (n = 4), Miniature

Table 1. Baseline characteristics according to treatment group.

Variable	Trilostane (n = 17)	Untreated (n = 26)	*P* value
Median age, years (IQR)	10 (9–13)	12 (10–12.8)	.50
Median weight, kg (IQR)	7.3 (5.4–14.5)	7.9 (5.3–10.9)	.56
Female, number (%)	10 (59)	18 (69)	.53
Median ALT, U/L (IQR)	98 (72–173)	91 (51–162)	.41
Median ALP, U/L (IQR)	1651 (1008–2363)	1303 (824–2387)	.69
Median pre-ACTH cortisol, μg/dL (IQR)	11.2 (7.7–17.3)	4.7 (3.7–7.7)	.006
Median post-ACTH cortisol, μg/dL (IQR)	36.4 (26.4–50)	31.4 (25.1–41.5)	.22
Hepatomegaly, number (%)	8 (47)	17 (65)	.34
Polyuria and polydipsia, number (%)	5 (29)	13 (50)	.22
Abdominal distension, number (%)	5 (29)	9 (35)	1
Alopecia, number (%)	6 (35)	6 (23)	.49
Panting, number (%)	2 (12)	4 (15)	1
Visit[a], number (IQR)	21 (11–36)	20 (8.8–27)	.35
Cost[b], US$ (IQR)	1554 (776–3502)	1262 (761–2110)	.51

IQR, interquartile range; ALT, alanine aminotransferase activity; ALP, alkaline phosphatase activity; pre-ACTH cortisol, cortisol concentrations before ACTH stimulation; post-ACTH cortisol, cortisol concentrations after ACTH stimulation.

[a]Apart from the monitoring visits.

[b]Apart from the cost of trilostane and its monitoring.

Dachshund (n = 2), Shih Tzu (n = 2), Pomeranian (n = 2), Beagle (n = 1), Chihuahua (n = 1), Miniature Pinscher (n = 1), Miniature Schnauzer (n = 1), Shiba (n = 1), Welsh Corgi (n = 1), and Yorkshire Terrier (n = 1); while those in the untreated group included Shih Tzu (n = 7), Miniature Dachshund (n = 4), Mongrel (n = 3), Welsh Corgi (n = 3), Chihuahua (n = 2), Miniature Schnauzer (n = 2), Papillon (n = 2), Yorkshire Terrier (n = 2), and Pomeranian (n = 1).

Median survival time for the trilostane group was not reached (95% confidence interval [CI], 443 days–not applicable) and was significantly longer than the 506 days (95% CI, 292–564 days; $P = .016$) for the untreated group (Fig 2). 2-year survival rates were 52.2% (95% CI: 20.3–76.7%) in the trilostane group and 8.5% (95% CI: 0.6–30.3%) in the untreated group.

In multivariate modeling, assignment to the untreated group (hazard ratio [HR], 5.01; 95% CI, 1.63–15.44; $P = .005$) was associated with a higher risk of death. On the other hand, age (HR, 1.04; 95% CI, 0.82–1.31; $P = .76$) and pre-ACTH cortisol (HR, 1.07; 95% CI, 1.00–1.15; $P = .065$) did not correlate with survival. The assumption of constant proportional hazards was correct for each variable. Similarly, a secondary analysis (which censored dogs on cessation of trilostane treatment) only identified assignment to the untreated group (hazard ratio, 4.39; 95% CI, 1.34–14.70) as associated with increased mortality.

Twenty-three of the 43 dogs were dead on the day of censorship. Although autopsy was not performed in any dogs in this study, suspected causes of death or reasons for euthanasia are summarized in Table 2. Only 1 dog, from the untreated group, was euthanized because of neurological signs. Although the cause of neurological signs of this dog was not apparent, the owner of the dog selected euthanasia because the seizures experienced by the dog could not be controlled.

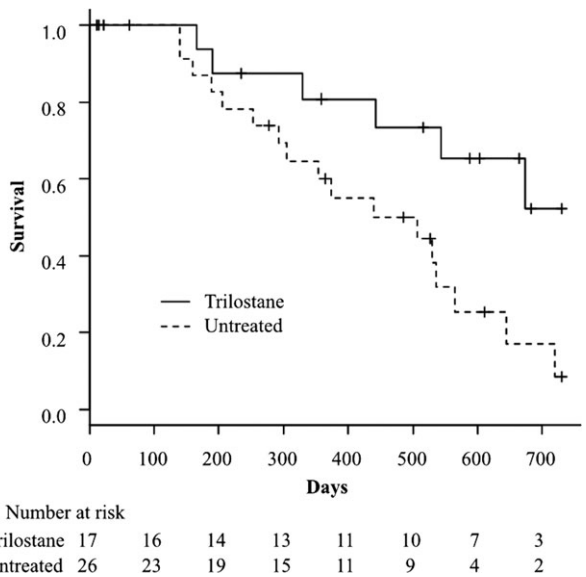

Fig 2. Kaplan–Meier survival curves for the trilostane group (solid line) and untreated group (dashed line). Median survival time for the trilostane group was not reached (95% confidence interval [CI], 443 days–not applicable), and was significantly longer than the 506 days (95% CI, 292–564 days; $P = .016$) for the untreated group.

Discussion

This study compared survival times of dogs with PDH that were treated with trilostane or were untreated. Although this study used a retrospective design, the results suggest the possibility that withholding treatment for PDH might be associated with a higher risk of death.

Several reports have described survival times in dogs with PDH treated by trilostane, with median survival times having been reported as 549 (n = 78), 662 (n = 123), 852 (n = 85), 900 (n = 40) and 930 (n = 43)

Table 2. Suspected cause of death or reason for euthanasia in the trilostane and untreated groups.

	Trilostane (n = 6)	Untreated (n = 17)
Cause of death		
Respiratory disease (dyspnea)	1	4
Diabetes mellitus	1	
Gallbladder mucoceles	1	
Chronic kidney disease	1	
Hemangiosarcoma	1	
Hepatic tumor		1
Osteosarcoma		1
Immune-mediated hemolytic anemia		1
Inflammatory bowel disease		1
Neurological signs		1
Heart disease		1
Pancreatitis		1
Unknown cause	1	5
Reason for euthanasia		
Neurological signs		1

days.[32–36] In our study, median survival time was not reached for the trilostane group during the study period. Because the trilostane group in our study included fewer cases (n = 17) with a small number of cases at risk after 2 years, we conducted survival analysis at 2 years.

On the other hand, no large-scale studies have reported untreated survival times in dogs with PDH in the past, so the impact of withholding treatment on survival has been unclear. In human patients with Cushing's syndrome, the prognosis without treatment is poor and the estimated 5-year survival is only 50%.[37] This high mortality rate is due to the complications associated with the disease, such as thromboembolism, cardiovascular disease, and infections. These complications largely depend on the effects of excess cortisol,[38,39] emphasizing the importance of correcting cortisol imbalances in Cushing's syndrome.[40] Multivariate analysis in our study found an association between the untreated group and a higher risk of death, indicating the possibility that withholding treatment might influence survival in dogs with PDH. Because autopsy was not performed in any dogs in this study, the cause of death was uncertain in most cases and associations with hyperadrenocorticism were not fully determined. Despite this, some deaths such as dyspnea, neurological signs, diabetes mellitus, gallbladder mucoceles, and pancreatitis might have been related to PDH. In particular, dyspnea was a frequent cause of death (1 in trilostane group, 4 in the untreated group) and might have been caused by pneumonia or pulmonary thromboembolism. This suggests the importance of correcting cortisol excess in canine PDH, as in human Cushing's syndrome. With Cushing's disease in humans, despite treatments, approximately 70% of deaths are due to cardiovascular disease or infection that might be associated with hypercortisolemia, indicating that the impacts of hypercortisolemia remain long after corrections of excess cortisol.[41] In dogs with PDH, the association between the duration of hypercortisolemia before treatment and survival has not been clarified. Furthermore, the causes of death for dogs with PDH have not been fully investigated. Further investigation of the causes of death and the relationships to the treatment of this disease are necessary.

In addition to the treatment group, we included age and pre-ACTH cortisol as factors in the multivariate analysis. Recent data have shown that old age and high levels of serum phosphate concentrations at diagnosis display significant negative associations with survival in dogs with PDH treated using trilostane.[36] Concerning age, other studies that included dogs treated with trilostane or mitotane have reported similar results.[33,35] In contrast, age was not reported to be associated with survival in another study that included dogs treated with trilostane, and our results are consistent with theirs.[32] The reason for this difference is not clear. In our study, differences may have been related to differences in case selection, because this study included dogs with PDH that were treated or untreated. In our study, plasma phosphate concentration was not available for most dogs and could not be investigated as a prognostic factor. In a previous study, pre-ACTH cortisol was not found to be associated with survival time in dogs with PDH treated using trilostane.[36] However, in untreated cases, excess cortisol may be related to survival time, considering that the high mortality rate of Cushing's syndrome in humans may be associated with the effects of excess cortisol.[38] We therefore included pre-ACTH cortisol as a factor in multivariate analysis. In fact, although pre-ACTH cortisol was not associated with survival in multivariate analysis, the survival time with a pre-ACTH cortisol above laboratory reference range (>7.2 μg/dL) was shorter than that with a pre-ACTH cortisol within reference range (≤7.2 μg/dL) when survival curves were compared in the untreated group alone ($P = .019$, data not shown). With regard to prognostic factors for this disease, especially in untreated cases, further study may be needed.

This study included dogs that were in middle and old age, and medium- and small-sized breeds, consistent with a previous large population study.[33] Poodles, which are known to be susceptible to PDH, were coincidently not included in this study. This may be attributable to differences in the popularities of these breeds among countries.

The rates of common clinical signs in dogs with PDH reported here were lower than in a past report. In a review of 3 past studies, the rates of hepatomegaly, polyuria and polydipsia, abdominal distension, alopecia, and panting in dogs with hyperadrenocorticism were 51–67, 80–91, 67–73, 60–74, and 30%, respectively.[2] Because appreciation of hyperadrenocorticism has been increasing recently, dogs are likely to be diagnosed at an earlier stage while clinical signs are still subtle.[21] Therefore, the current cases may have tended to have milder clinical signs than cases seen in past studies. Additionally, primary-care hospitals tend to encounter

the cases that have mild clinical signs. Past reports on dogs with PDH have almost all been conducted at academic medical centers and thus might have included more complex cases.

The major limitation of our study was that the decision of whether to pursue treatment was not assigned randomly. Performance of a randomized placebo-controlled trial is difficult, given that withholding treatment that is considered effective is unethical. We conducted a retrospective study in which the decision to provide treatment was determined by the clinician and owner based on clinical signs, adverse effects of treatment, and cost. Median pre-ACTH cortisol was higher in the trilostane group than in the untreated group, suggesting that a group assignment bias could have been present. One possibility was that dogs in the trilostane group may have shown more severe clinical signs related to higher pre-ACTH cortisol than those in the untreated group and therefore may have been more likely to be treated. Because of the nonrandomized design, this study needed to correct for the influence of confounding variables, but relatively few variables could be included in a multivariate model due to the small population. As a result, not all confounders could be eliminated. In particular, factors such as whether euthanasia was performed, whether treatment was being performed for concurrent illnesses, and severity of clinical signs were not included in the analysis. However, these factors were considered unlikely to have affected the results. This is because all dogs apart from 1 died of their diseases and no dogs in this study were euthanized because of reasons unrelated to the disease, and no significant differences were seen between groups in terms of the number of visits to the hospital, cost of all treatments, or the rate of clinical signs. In addition, because of the retrospective nature of the study, some variables that might represent predictors of survival in this disease, including serum phosphate concentrations,[36] pituitary gland size,[42] and plasma ACTH concentration[42] were not available for many dogs. Moreover, other concurrent illness was not an exclusion criterion in this study. Because of the retrospective design, fully assessing whether concurrent illnesses were present and whether concurrent illnesses were associated with PDH was difficult. Finally, the fact that such a high number of dogs were censored because of loss to follow-up, particularly in the treatment group, decreased the reliability of the survival analysis. A prospective study with a larger population is thus needed in the future.

This retrospective cohort study suggests that withholding treatment for dogs with PDH might be associated with a higher risk of death. To the best of our knowledge, this represents the largest study to date to report survival times of untreated dogs with PDH. However, further evaluation of the influence of withholding treatment and prognostic factors in this disease is needed in a prospective study with a larger population.

Footnotes

[a] Cortrosyn; Daiichi Sankyo, Tokyo, Japan
[b] Corson P; Nippon Zenyaku Kogyo, Fukushima, Japan
[c] LSI Medience, Tokyo, Japan
[d] Monolis, Tokyo, Japan
[e] Immulite 1000; Siemens, Tokyo, Japan
[f] Vetoryl; Dechra Pharmaceuticals, Northwich, UK
[g] Adrestan; Kyoritsuseiyaku, Tokyo, Japan

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Conflict of Interest Declaration: Authors disclose no conflict of interest.

Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

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